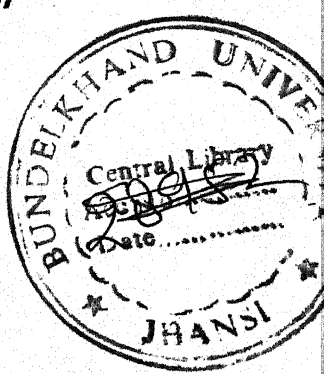
MATHEMATICAL MODELS IN MEDICAL RESEARCH : SOME APPLICATIONS OF STOCHASTIC PROCESSES

THESIS SUBMITTED FOR THE DEGREE OF
Ph. D. (STATISTICS)

BY

B. L. VERMA
M. A (Stat.)
Statistician-cum-Lecturer,
Department of Social and Preventive Medicine,
M. L. B. Medical College,
JHANSI (U. P.)



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CERTIFICATE

This is to certify that the present work entitled, "Mathematical Models in Medical Research : Some Applications of Stochastic Processes" has been carried-out by Sri B.L. Verma, Statistician-cum-Lecturer in the Department of Social and Preventive Medicine, M.L.B. Medical College, Jhansi (U.P.) under my direct guidance and supervision. The results derived by him have been checked and verified by me from time to time.

The Thesis fulfils the regulations governing the submission of Thesis for the degree of Ph.D., laid down by the Bundelkhand University, Jhansi (U.P.).

S.K. Ray

Date : April 5, 1981.

(S.K. RAY)
Ph.D.,
Professor and Head,
Department of Statistics,
Lucknow University,
LUCKNOW (U.P.)

(SUPERVISOR)

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Date : April 5, 1981.

(R.N. SRIVASTAVA)
M.D.(Hons.),D.P.H.,D.I.H.,F.A.M.S.,
F.I.S.C.D.,F.I.P.H.A.,F.N.I.E.,
F.R.I.P.H. & H.(London),
Professor and Head,
Department of
Social and Preventive Medicine,
M.L.B. Medical College,
JHANSI (U.P.)

(CO-SUPERVISOR)

PREFACE

P R E F A C E

An important fundamental aspect of any physical science is the formulation and/or development of models so as to understand the universe in which man finds himself. It also characterizes his attempts at understanding the inter-related complex of biology as a whole, including medical science. Now-a-days, one can hardly imagine a scientific subject which does not depend upon some sort of mathematical modelling to aid in the solution of the vast array of problems and in getting some insight into the important and essential underlying relationships.

Development of mathematical models and their application in various disciplines of medicine and health, particularly in epidemiological research, are essential to investigate the mechanisms of different phenomena and to study relationships amongst factors inherent therein. Application of models, construction of which considers relevant and important factors, provides appreciable values to many important epidemiological parameters. In recent years, a considerable advancement has been made in the

application of models by incorporating stochastic mechanism of one kind or the other in them. In such models, for example, the knowledge of a system being in a certain state at one specific time does not determine uniquely its state at other timings but merely the probability of possible states.

The present work deals with the formulation and application of some stochastic models for studying certain epidemiological aspects of malaria, a disease having considerable role in the overall morbidity and mortality conditions in India. The complete work has been presented in different Chapters.

Chapter I elaborates upon the significance and need of the development of mathematical models and their application in medicine, particularly in malaria epidemiology, and the objective of the present work. Chapter II discusses the concept of mathematical modelling, kinds of existing models and their utilities in different areas of medicine and health. In Chapter III, a brief account of the epidemiology of malaria along with a review of available models, evolved and applied to study epidemiological aspects of malaria so far has been given. An attempt has been made to point out the lacunae in available malaria models and to stress the need of the formulation of stochastic models for

studying certain epidemiological patterns of the disease, keeping in mind the situations and facilities available in our country. Chapter IV deals with a stochastic model for estimating malaria parasite incidence rates and force of infection in infants; it also illustrates the use of Life Tables in estimating such parameters.

Models, based on stochastic processes, for estimating daily malaria parasite incidence and recovery rates and transition probabilities from one state to the other in general population from longitudinal data, considering different situations have also been studied. Chapter V shows a stochastic model, based on two states only, viz., malaria positive state and malaria negative state, to estimate daily net malaria parasite incidence and recovery rates and transition probabilities in general population. The presence of one more risk, namely 'risk of lost to follow-up' has been taken into consideration in Chapter VI while estimating such malaria transition rates from one state to the other. This model considers 3 states of malaria and thus provides daily gross malaria parasite incidence and recovery rates in general population. In order to judge their suitability, these models have also been applied to the

observed data. Chapter VII, however, deals with 7 mutually exclusive states of malaria considering a more general case. It discusses a probability model to estimate species - specific malaria transition rates in the presence of the risk of the 'lost to follow-up' in the general population.

Since relevant data from follow-up studies on malaria could not be found in the literature, a door-to-door follow-up survey in two villages of Jhansi district (U.P.) was carried-out on presence or otherwise of malaria parasites in the blood; to make it possible to judge, as far as possible, the applicability and suitability of the evolved models. The details of the methods of survey and population covered etc. have been given in Chapter VIII. Chapter IX demonstrates the application of stochastic processes in estimating the additional years of life that would be saved by an individual if malaria was eradicated from India.

It is hoped that this work would be of some use to epidemiologists, malariologists and to many others working on the subject. Methods outlined here are expected to facilitate the problem of quantitative assessment of malaria situations in specific population groups.

The present work would not have been possible without the guidance of and help from many, and I find it most pleasant to remember and record my obligations to them.

I express my deep sense of gratitude to my revered teacher, Professor S.K. Ray, Ph.D., Head of the Department of Statistics, Lucknow University, for his persistent intellectual guidance. It has been a matter of great pleasure for me to have worked under an academician of his repute. In spite of being at such a distance from the field of the work, he rendered his constant erudite guidance. A debt like this one can hardly be paid off in words.

I am highly obliged to Professor R.N.Srivastava, M.D.(Hons.),D.P.H.,D.I.H.,F.A.M.S.,F.I.S.C.D.,F.I.P.H.A., F.N.I.E.,F.R.I.P.H. & H.(London), Head of the Department of Social and Preventive Medicine, M.L.B. Medical College, Jhansi (U.P.), my Co-Supervisor. His wide experience in research in different areas of medicine, particularly on applications of mathematical models in epidemiology and his keen interest in the changing pattern of epidemiology of malaria has been instrumental for me in carrying-out this work. His day-to-day guidance on various aspects of the disease made it possible to introduce rationality in models.

Dr. G.D. Shukla, M.D., Lecturer in Psychiatry, M.L.B. Medical College, Jhansi (U.P.) has been of immense help in the completion of this work. His valuable comments and fruitful criticisms have greatly contributed towards the final shape of the presentation. I wish to record my grateful thanks to him.

I wish to acknowledge my heart-felt thanks to Professor K.B. Pathak, Ph.D., of the International Institute for Population Studies, Bombay, who stimulated me to work on the present subject, made some relevant literature available and was always available for discussion on the solution of hurdles arising during the course of the work. I wish to place on record my gratefulness to him for his kindness.

I express my sincere thanks to Dr. Arun Kumar, Reader and Dr. M. Saran, M.O.H. cum Lecturer, Department of Social and Preventive Medicine, M.L.B. Medical College, Jhansi (U.P.), for providing facilities and help in the field work and in the examination of blood slides for malaria parasites.

Thanks are also due to Dr. Amerjeet Singh and Dr. Jai Pal Singh, Demonstrators, to the field staff and to the medical interns, then posted in the

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Dated : April, 5, 1981.

Place : Jhansi (U.P.).

(B.L. VERMA)

I N D E X

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CHAPTER I

INTRODUCTION

INTRODUCTION

Health is a very important phenomenon of the human population and the improved health status is an accepted goal of the communities and nations. Health status of the population in a community is determined by a variety of factors. Further, it is affected by the various diseases prevalent therein. Assessment of health conditions by evolving quantitative measures in the developing countries like India, where people are thought to have poorer health than their counterparts in developed countries, is essential because of many likely reasons.

Use of sophisticated mathematical methods such as - mathematical models, in different areas of medical research is often appreciated in studying various aspects of the diseases and the associated phenomena. Now-a-days in medical research, mathematical models are frequently used in the assessment of mortality and morbidity conditions in a population, in the measurement of health-levels in a community, in studying dynamics of diseases and efficacy of drugs, and in the planning as well as in evaluation of health programmes. The development of

models, using stochastic processes in different disciplines of medicine and health, however, is a newer concept.

The theory of stochastic processes plays an important role in the investigation of random phenomena depending on time. Since the early work of Kolmogorov (1931) and Feller (1936), the theory of stochastic processes has shown a constant development. Main development, however, in its theory and applications took place during the last 3 decades. Stochastic processes have been used to describe empirical phenomena and to solve many practical problems. Its field of application is considerably expanding day by day and at present, such processes are being applied in almost every field of human life. In medicine and health too, use of such processes is progressively increasing with time.

In medicine, a good amount of work on the development of mathematical models and their application has been done in recent years. However, the available models, evolved for different purposes, consider generally deterministic approaches and the random component in the process of their development has seldom been taken into account. Thus, very few mathematical models based on stochastic processes

have been evolved in different areas of medicine and health and the application of stochastic theory to the study of empirical problems, associated with the various aspects of diseases and ill health, particularly by Indian workers has been almost negligible hitherto. Therefore, there seems a need to study the mechanism of various phenomena of medicine, particularly, the epidemiological aspects of different diseases quantitatively by applying stochastic processes.

Malaria, in India, has been a great problem for many years. Despite the implementation of alternative strategies under National Malaria Eradication Programme, the positive cases of malaria increased significantly with time during the recent decade. Government of India, seeing the role of the disease in the overall morbidity and mortality conditions and ultimately, its impact on health of the people and on economy of the country, had decided to invest a considerably high proportion (40%) of the total health budget* for 1979-80, to control the malady. Many new projects at macro and micro levels in the country have been initiated to evolve suitable strategies to control the disease in the shortest period of time. The epidemiologists and the

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* Source : The Hindustan Times, August 1, 1980.

bio-statisticians are engaged in developing new measures to study different aspects of the disease so as to control the disease effectively. Thus, under the present circumstances, the study of various epidemiological aspects of malaria with the help of stochastic processes would appear to be a relevant subject to deal with.

In the present work, an effort has been made to formulate certain models of malaria, utilizing stochastic processes and to apply them to the actual malaria situations in a defined population. Values of some important epidemiological parameters, such as – malaria parasite incidence rate, force of infection of the disease acting on a population at a particular time and malaria recovery rates etc have been estimated. Methods have been devised to study daily malaria parasite incidence and recovery rates from longitudinal data considering 3 different empirical situations, viz., (i) when cases studied initially for malaria are covered, in toto, during subsequent follow-ups, (ii) when a few cases are 'lost to follow-up' and (iii) when risk of 'lost to follow-up' is present in the population and such rates are to be estimated for specific malaria species. Estimation of additional years of life that an individual could be expected to

live if the risk of malaria were eliminated from the population in India has also been carried-out on the basis of 15 years epidemiological data of the country, considering various assumptions.

Further, since relevant data at certain occasions to illustrate the application of the suggested stochastic models were not available in the scientific literature on the subject, a door-to-door investigation on malaria in a rural population of Jhansi district (U.P.) was also carried-out. Investigation conducted in the area, consisted of two consecutive follow-ups of the available population, besides their initial study for the presence of malaria parasites in the blood or otherwise. The observations are discussed in the light of associated lacunae with the methods, if any.

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CHAPTER II

BRIEF REVIEW ON MATHEMATICAL MODELLING IN MEDICINE

BRIEF REVIEW

ON

MATHEMATICAL MODELLING IN MEDICINE

In recent years, there has been an increasing use of sophisticated mathematical/statistical techniques and methods in various disciplines of medicine and health. Advanced methods and new tools such as - operation research, system analysis, multifactorial approach, cost-benefit analysis and mathematical models etc have been developed and utilized in planning and execution of epidemiological investigations (Cvjetanovic et al, 1971; 1972; Grab and Cvjetanovic, 1976; Nair, 1977), clinical trials (Gupta, 1978) and therapeutic research (Martin, 1962); in studying different aspects of demography and health of the people (Pathak, 1970; 1973; Romeder, 1977); in prediction and simulation of trends of diseases under different epidemiological conditions (Indrayan et al, 1970; Lechat et al, 1977); in the assessment of the effectiveness of various health strategies (Uemura et al, 1971; Grab and Cvjetanovic, 1975; 1976) and in the assessment of various preventive and control measures against specific diseases (Lechat et al, 1978) in different population groups.

However, the development of mathematical models and their applications in the different areas of medicine and health, especially to the epidemiology of infectious diseases are rather newer concepts. Their construction and application to the epidemiology and control of tropical diseases was initiated by Ross (1908) about 72 years ago; and since then, some important contributions have been made on the subject. However, the literature is still scanty and the subject is in its early phase of development. Recently, it has been pointed-out (Srivastava, 1975) that, practice of community health should be based on solid foundation of epidemiologic, ecologic and demographic analyses and such aspects should be studied by developing and applying relevant mathematical models. Hitherto, very little use has been made of these concepts and techniques in designing, administering and evaluating community health services in developing countries like India (Srivastava, 1975). Mathematical models have great potentialities and, in fact, are very important tools for the practitioners of community health.

2.1 DEFINITION OF MODELS.

Mathematical models may be defined as the expressions involving mathematical relationships -

either equations or inequalities - representing variables and parameters that define a particular phenomenon. Of late, there has been growing literature on theoretical modelling and some models have been constructed and used for varied purposes in different disciplines of medicine and health. The literature on the subject, however, is very variable in content and more extensive than one might imagine.

2.2 TYPES OF MODELS.

The classification of mathematical models on the basis of a sound scientific reasoning is not possible in view of their wide complexity. They may, however, be categorized into following groups considering their mode of construction, nature and uses in various fields. Here, it may be stressed that these groups are not mutually exclusive and, in fact, overlap each other to certain degree. Thus, a particular model may be put easily in more than one category. This classification has, therefore, been introduced solely for the sake of convenience in the description. An extensive description of all the models evolved hitherto is beyond the present scope and can be seen elsewhere (Verma et al, 1980 a); only broad groups will be discussed with the help of relevant illustrative examples.

(I) Descriptive models

Models which simply summarize or describe a set of data in few numbers or in terms of simple mathematical relations are called descriptive models. Such models do not attempt to elucidate the mechanism of a system nor predict future course of the phenomenon. These models are useful in the diagnosis of community for health problems and other epidemiologic researches.

A descriptive model for studying the relationship between performance or output of the maternity care system amongst local authorities in England and Wales and corresponding input of medical and ancillary resources has been suggested recently (Ashford et al, 1973). It considers 88 descriptive variables, representing characteristics and general environment of each local authority. The model, besides providing many important epidemiologic findings, indicates a close relationship between performance measure and descriptive variables. A similar model has been proposed for identifying environmental indicators significant to community health (Bertrand et al, 1979). After application to a study of child mortality, it has been found to be very useful in monitoring and health care planning.

(II) Predictive models

These models elucidate the mechanism of a phenomenon and predict future courses of systems. Such models are, sometimes, also called simulation models. Prediction by these models is based on the assumption that the future dynamics of different forces will conform to the present happenings; they do not take into account other unknown forces entering the scene at the later dates. Simulations are made from mathematical equations, derived from the 'Flow Chart' - showing graphical representation of the mechanisms of phenomena or transmission dynamics of the diseases. Suitable epidemiological information is used to provide values to different independent variables to simulate desired results.

In fact, majority of the models evolved, aim to make predictions in one way or the other, irrespective of the approaches in their construction. Models developed by Uemura et al (1971), Cvjetanovic et al (1971; 1972), Dietz (1976 a) and Grab and Cvjetanovic (1975) for cholera, typhoid fever, tetanus, infectious diseases and cerebro-spinal meningitis respectively, are a few examples of such models.

(III) Probabilistic and stochastic models

A random phenomenon is defined as an empirical phenomenon that obeys probabilistic rather than deterministic laws. Randomness, however, may be of two sorts - true randomness, and pseudorandomness (Lucas, 1964). True randomness is seen where it is impossible to provide any ultimate explanation as to why a given value should take place instead of the other. At certain instance, however, random characteristics of the phenomenon are observed because of our failure to take certain factors into account while designing experiments, interpreting results and building mathematical models. Such randomness is labelled as pseudorandomness or 'ignorance engendered apparent randomness'.

A probabilistic model is one whose construction is based on random approach; involving true randomness or 'ignorance engendered apparent randomness'. Such models usually deal with a single random phenomenon at a time. The models of Newell (1954) and Pike et al (1963) evolved for the efficient planning of casuality wards in a hospital are examples of such models.

Further, a random phenomenon that arises through a process which is developing in time in a manner controlled by probabilistic laws is called

stochastic process. Indeed, the word 'stochastic' is of Greek origin (Hagstroem, 1940). In seventeenth century English, the word 'stochastic' had the meaning "to conjecture", "to aim at a mark". It is however not quite clear how it acquired the meaning it has today of "pertaining to chance". A few people use 'chance process' or 'random process' as the synonyms of 'stochastic process'.

Stochastic processes are, in fact, dynamic parts of probability theory in which one studies a collection of random variables from the point of view of their interdependence and limiting behaviour (Bailey, 1964). Mathematical models which deal with stochastic processes are known as stochastic models. In other words, probabilistic models where the phenomenon involves many random variables are called stochastic models. Development of these models is essentially based on a set of assumptions which, inter alia, ensure random behaviour of the system involved. Stochastic models, at times, are difficult to handle in full details, particularly when situations are non linear in nature such as epidemics (Bailey, 1980). Examples of such models are those developed by Hillis (1979) and Verma et al (1980 b, 1980 c) for infectious diseases and malaria, respectively, and by Gupta (1978)

for follow up of I.U.C.D. clinical trials. Survival models developed by Beck (1975; 1979) are also of this sort.

(IV) Deterministic models

Models whose formulation is based on completely deterministic approach are known as deterministic models. Obviously, construction of these models does not assume any type of randomness. Since the behaviour of most of biological phenomena may be regarded as deterministic, such models have relatively wider range of applicability. Further, deterministic models can be easily used in non-linear situations also.

Many models of this kind have been formulated in medical science and used in its different disciplines. The models of Muench (1959), used by Srivastava et al (1971) and Indrayan et al (1970) for the assessment of infective force of filariasis and of Dietz et al (1974) and Dietz (1976 b), developed for malaria and helminthic diseases respectively, are examples of such models.

(V) Operation research models

Operation research is the scientific study of effectiveness of operations; an operation being defined

as a human activity in which certain set of means is directed to achieve a specified goal. The models, aimed to design the operations to achieve specified effectiveness are known as operation research models. Such models suggest how the effectiveness of operations can be maximized. In these models, effectiveness of operations is measured with the help of various indices such as cost-benefit ratio, probability of occurrence of a favourable event, ratio of present performance to the past and time rate of out-put etc.

Many operation research models have been built for their use in health planning and management of hospitals. Kramer et al (1979) and Hutchinson et al (1979) suggested operational research models for the assessment of adverse drug reactions (ADR). The model (Kramer et al, 1979) is arranged in an algorithm from which emerge scores for six axes of decision strategy. The sum of scores, ordinarily partitioned, allows one to rate candidate's ADR as - definite, probable, possible or unlikely. A similar model has also been brought-forth by Singh et al (1978) for holding down the cost of hospitals and clinics.

(VI) Diagnostic models

In clinical medicine, diagnoses of patients depend upon clinical judgement arising from subjective impressions and previous experience of individual clinicians. Because of many points being in favour and against for a disease in a patient, it sometimes becomes extremely difficult for a clinician to apply right judgement for the diagnosis. In order to introduce objectivity and thus, to make accurate diagnosis, many models have been suggested and are in use. Such models are known as diagnostic models. These models are formulated by assigning suitable scores, in order of importance, to various signs and/or symptoms. The sum of scores of a patient are grouped suitably to indicate presence or otherwise of a certain disease or condition. Such models facilitate clinicians to diagnose patients for a certain disease at least in probability.

Diagnostic models for many diseases such as - rheumatic fever (Jones, 1944; American Heart Association, 1955), hyperthyroidism (Wayne, 1960) and endogenous depression (Corney et al, 1965) have been suggested and are being used widely.

(VII) Rational models

Models, derived in a logical way, starting from basic observational knowledge, theory and reasonable supposition about physical components of a system and their behaviour are known as rational models. Such models, often predict parametric values of a phenomenon for different values of independent variables, even for those which fall beyond the range of data. Further, the best predictability is attained by introducing rationality in models, as much as possible. The model developed by Uemura et al (1971) for cholera, Dietz et al (1974) and Molineaux et al (1978) for malaria and by Cvjetanovic and Grab (1976) for whooping cough may be regarded as rational models.

(VIII) Empirical models

An empirical model is one, chosen with little regard to the characteristics of the system but having enough flexibility to reflect sufficiently and faithfully the main features of available data. Such models may lead to bad predictions particularly, for those values of independent variables which fall beyond the limits of data but have been used to fit the model.

The examples of empirical models may be taken as polynomials of various sorts, relating a

dependent variable with many independent ones. More specifically, models of Verma et al (1977), used to predict malaria endemicity in terms of various metereological conditions in Jhansi district of Uttar Pradesh and of Chaurasia and Pattankar (1979) for detecting hypertensive patients in a group of people may be regarded as empirical models.

Since beyond a certain point, empiricism enters in almost all the models because of lack of perfect basic observational knowledge, theory and supposition, all mathematical models have both - rational and empirical aspects.

2.3 UTILITY OF MATHEMATICAL MODELS.

The public health importance of mathematical models is very high, indeed. They are important tools for the practitioners of community health. Models in different disciplines of medicine and health have been used for varied purposes. Some important areas of their application are outlined as under.

(I) Epidemiologic research

Significance of models in epidemiology has recently been indicated by many workers (Muench, 1959; Srivastava, 1975; Dietz, 1977). Epidemiology as the

scientific basis of disease prevention and control, has to explain prevalence and incidence of diseases as the function of the corresponding risk factors. For instance, in case of communicable diseases the key risk factor is the contact rate per individual per unit of time. Only those contacts are counted which are potentially infective. There may be direct person to person encounters or these may be made via disease vector. The main result of the theoretical epidemiology is a threshold condition, according to which the contact rate has to exceed a critical value for the stable maintenance of an endemic disease distribution. The critical contact rate is taken to be equal to the inverse of the duration of the infectious period of a case.

The aim of epidemiology can be viewed as the quantification of individual factors of the reproduction rate such as duration of infectious period, man-biting rate and probability of an infection given a contact etc. Here, reproduction rate means the number of secondary cases, generated by one case during his entire infectious period. An estimate of the magnitude of the reproduction rate allows one to assess the efforts required to control or to eradicate the disease. If the objective is control (i.e. reduction to a 'tolerable'

level), then one needs to know the relationship between endemic level and the reproduction rate. This problem can be precisely approached by using the concept of mathematical modelling.

Recently, many workers (Muench, 1959; Wright, 1960; Indrayan et al, 1970; Cvjetanovic et al, 1972; Rao et al, 1974, Dietz et al, 1974; Grab and Cvjetanovic, 1975; Zimmer and Puskin, 1975; Dietz, 1975; Berger, 1976; Anderson, 1976; Dietz, 1976 a; Lechat et al, 1978) have designed and used models to study epidemiological aspects of various diseases.

A conceptual model developed by Wright (1960) has been utilized by Pless et al (1972) to suggest chronic physical disorder as an important condition in children which affects their concept, their behaviour and ultimately their mental health, thus identifying them as 'high risk' group for psychological disorders. This model further suggests that this sequence is influenced by other factors in child's social environment amongst which the functioning of the family unit is of major importance. Thus, within this 'high risk' children, a group was identified for the allocation of limited community resources for preventive mental health services.

A reversible catalytic model suggested by Muench (1959) has been used by Indrayan et al (1970) and Srivastava et al (1971) to assess the endemic force of filariasis in specific and concrete terms. The endemicity levels of the disease of two areas at the same time and also of the same area at two different times, the latter of which may indicate the efficiency of control measures in operation against the disease in the area, were compared. The reversible catalytic model described the situation more closely to the observed data in two areas - rural and urban (Srivastava et al, 1971).

Epidemiological features of many diseases such as - cholera (Uemura et al, 1971), tetanus (Cvjetanovic et al, 1972), malaria (Dietz et al, 1974; Molineaux et al, 1978), whooping cough (Cvjetanovic and Grab, 1976), helminthic diseases (Dietz, 1976 b), cancer (Fears et al, 1977) and leprosy (Lechat, 1971; Lechat et al, 1974; 1977; 1978) etc have been studied by evolving relevant mathematical models.

(II) Predictions

Considerable utility of mathematical models lies in their predictive behaviour. Almost all models, by and large, predict the values of some important

parameters. Predictions through mathematical models, however, assume that the future dynamics of different forces will conform to the happenings of the past and present and do not take into account other unknown forces entering the scene at a later date. The epidemiological information utilized in the model for the purpose of prediction need to be reliable and representative of the population to which it relates.

Cvjetanovic et al (1972) used their model to simulate the incidence of and death rates from tetanus in immunized and un-immunized groups of new borns and in general population. After choosing suitable values of some epidemiological parameters such as - vaccine coverage, vaccine effectiveness and initial level of endemicity, they predicted likely values of above parameters in successive years after vaccination.

Berger (1976) evolved a model to study the number of foxes to be immunized to stop further spread of rabies in an area under certain assumptions. He utilized his model to simulate the weekly incidence of rabies in relation to the population density of foxes in a specified area.

Prediction of annual incidence of typhoid, proportion (%) of susceptibles and of carriers, daily

force of infection and death rates from typhoid etc have been made recently (Cvjetanovic et al, 1971). Similarly, leprosy control costs (Lechat et al, 1978) and incidence rates of infectious diseases under the influence of seasonal fluctuations (Dietz, 1976 a) have also been simulated with the help of mathematical models.

(III) Planning of preventive and control measures

International and national health agencies aim to prevent, control and eradicate, as far as possible, the important diseases and thus, to enhance the present level of health of the individuals. For the diseases in which special programmes are in operation, there are alternative methods of their prevention viz. immunization, sanitation, health education and other prophylactic measures and of control such as chemotherapy and/or vector-control. The question often asked by health planners calls for advice on an 'optimal' allocation of resources to the various preventive and control measures available. Often, however, it is not specified what should be optimized : whether control, for instance, is aimed at reduction in infection, disease, mortality or incidence. Given an explicit target, mathematical models can profitably be used to specify best methods of achieving it.

Recently, utility of mathematical models in planning of health programmes has been demonstrated by many workers (Newell, 1954; Pike et al, 1963; Cvjetanovic et al, 1971; 1972; Grab and Cvjetanovic, 1975; Srikantaramu et al, 1976). Utilizing hospital data, Newell (1954) and Pike et al (1963) predicted the number of beds that would be required in a casuality ward, giving proper allowance to the random fluctuations in the admissions. Their models were found useful in the planning of a casuality ward effectively. Similarly, models evolved by Cvjetanovic et al (1971; 1972) have been found very useful in the organization of preventive and control measures such as - anti-tetanus and anti-typhoid immunization and sanitation programmes etc.

(IV) Evaluation of preventive and control programmes

Mathematical models allow one to simulate the time course of prevalence and incidence of diseases which are expected for effectiveness of control measures. These simulations can then be compared with the actual observations in order to estimate the actually achieved effectiveness of control measures/or to test the model. The latter objective applies to the situations where the model has been fitted to the base

line data only, such that one can not be sure how well the model would be able to extrapolate the transmission under the influence of control measures. Thus, a careful evaluation of control programmes can improve the model for the benefit of subsequent control programmes. A model is useful only when it can make verifiable predictions which may even lead to its rejection. This procedure allows scientific progress to be made.

Evaluation of effectiveness of health strategies of different health programmes, of necessity, by mathematical models, has been demonstrated by different workers for various infectious diseases, viz., tetanus (Cvjetanovic et al, 1971), cholera (Uemura et al, 1971), typhoid (Cvjetanovic et al, 1972), whooping cough (Cvjetanovic and Grab, 1976) and leprosy (Lechat et al, 1977; 1978). Uemura et al (1971), for instance, studied many possible strategies for the control of cholera, such as - vaccination, sanitation, chemoprophylaxis and all possible combinations of these three strategies. They, for this purpose, evaluated each strategy by predicting incidence rates of cholera in next 10 successive years.

A stochastic model (Gupta, 1978) based on multiple decrement Life Table technique with competing

risks was constructed recently. This model has been applied to study the experience of a group of Indian women who had accepted I.U.C.D. This model facilitates the prediction of retention rates and expectancy of I.U.C.D. life by taking into account the fraction of a month spent by a woman and treating 'loss to follow up' as a competing risk. It has been advocated that this model can well be used for the evaluation of follow-up I.U.C.D. clinical trials.

(V) Measurement of level of health

A population is generally considered to have a level of health which rises or falls over time. In our society, health is positively valued and improved health status is a desired goal of communities and of the nation. Health, as defined by World Health Organization (W.H.O., 1958) is conceptually a wide term and because of the fact that the notion of health levels is difficult to define precisely, the development of an index for measurement of health accurately, has been a problem since long.

Traditional measures of the levels of health of a population, such as - morbidity, mortality, expectation of life and counts of health service activities etc are useful but have their own

limitations. Accurate and reliable measures of health of the community are needed to study the cost and benefit of the various community health programmes. In spite of numerous conceptual difficulties (Sullivan, 1966) in developing an index of health, Chiang and Cohen (1973) constructed a mathematical model for the purpose. This model, it looks, would measure the level of health of a population precisely.

(VI) Assessment of risk of getting a disease/infection

Information on the risk and the past and present evaluation of a disease in a community is essential for a valid description of the disease, predicting both - risk and prevalence of the disease in different population groups. A simple mathematical model based on various French epidemiological data on tuberculosis has been constructed by Lotte and Uzan (1973) to calculate the estimated annual risk of tuberculosis in a population. They utilized these estimates to compare the risk for two years - 1960 and 1970 and also predicted the same for the year 1980.

Verma et al (1980 b) developed a model, utilizing stochastic approach to estimate force of infection or risk of getting parasitaemia in infants

which was considered constant in nature. An assumption was, however, made that this constant force of infection can directly be measured in terms of effective contacts per susceptible infant per unit of time, no matter how complex the events leading to these contacts may be, and that the evidence of effective contacts is proved by blood smear positivity for malarial parasites. The model which is simple to understand and easy to use also enables authors to estimate age-specific malaria parasite incidence.

Similarly, a model of transition between causes of death over a given period of time has been constructed (Damiani and Aubenque, 1975). Ten major causes of death were chosen and the transition probabilities from one to the other causes of death between 1954 and 1962 for two sexes were worked-out. Ultimately, absolute probabilities by sex and causes of death in two years 1954 and 1962 were estimated.

(VII) Cost-benefit analysis

The results of control measures against the diseases, obtained by simulations are, indeed, of great significance. However, such results can not be judged on the basis of the effect of control measures on incidence rates only. The relative costs and

benefits have also to be taken into consideration since public health administrators will apply only those measures which are economically sound and feasible. In order to respect economic and logistic constraints, the effect of each measure and its cost should be examined to determine its merits and advantages.

In order to carry-out cost/benefit analysis of any control programme, say, immunization against a infectious disease, the costs of immunization and treatment must be known. The expenses incurred on immunization are considered as cost and saving in treatment derived from prevented cases as benefits. Cost/benefit analysis is, therefore, based on the comparis-ons of the money-values of the two components and their difference represents the net benefit. Further, in principle, at the time of cost/benefit analysis, the total social cost of the disease and not the cost of treatment only, should be taken into account (Cvjetanovic, 1974).

Recently, mathematical models have been utilized in the cost/benefit analysis of different control programmes in respect of many diseases, Viz., typhoid (Cvjetanovic et al, 1971), cholera (Uemura et al, 1971), tetanus (Cvjetanovic et al, 1972), cerebrospinal

meningitis (Grab and Cvjetanovic, 1975) and whooping cough (Cvjetanovic and Grab, 1976) etc. As an example, Cvjetanovic et al (1972) have studied costs and benefits of 4 alternative control programmes for tetanus, viz., (i) one mass vaccination, (ii) three mass vaccinations at 10-year intervals, (iii) vaccination of pregnant women, (iv) vaccination of pregnant women and 3 mass vaccinations at 10-year intervals. They, for each alternative control programme, predicted effects of the preventive measures on the global incidence rate of tetanus cases, cumulative costs of the immunization programmes and the cumulative benefits accruing from the savings on treatment costs. It was concluded, with the help of model, that control programme (iii), namely, vaccination of pregnant women, is the optimum one as benefits vis-a-vis costs are relatively more than other 3 control strategies.

(VIII) Diagnosis of patients

Mathematical models have been found to be of immense help in diagnosing many diseases. Diagnosis of rheumatic fever, for instance, is based on many complex points. Jones (1944) developed a diagnostic model and suggested a set of combinations consisting of different minor and major criteria to conclude about the correct diagnosis of rheumatic fever. Wayne (1960)

formulated a model to distinguish euthyroid cases from toxic ones, on the basis of weighted scores for 13 best discriminatory items, derived from discriminant function analysis. Patients scoring less than 8 were diagnosed as euthyroid, those scoring more than 11 as toxic whereas score of 9-10 denoted a doubtful diagnosis.

Similarly, Apgar (1953) formulated a diagnostic model for clinical scoring for asphyxia neonatorum which has been found to correlate well, both - with immediate prospects of survival and the likelihood of permanent brain damage. In the model, score of 10 denotes an infant in excellent condition while a gravely asphyxiated infant would be assigned a score of zero. A score below 6 indicates respiratory distress and urgent need of treatment. A diagnostic model has also been designed for endogenous depression and its response to E.C.T. (Corney et al, 1965).

(IX) Maximizing effectiveness of operations

As indicated earlier, mathematical models developed on operation research approach, maximize the effectiveness of human operations for attaining a specified goal within available resources. Srikantaramu et al. (1976) developed an operational model to indentify the problems of District Tuberculosis Programme in India. This model suggests

as to which class of functions has to be varied for better objective fulfilment. Besides enabling authors to compare effectiveness of two major activities - case finding and treatment at peripheral health institutions, it also suggests ways to enhance case finding efficiency and improvement in treatment activities.

Further, Nair (1977) has broughtforth many points to emphasize that National Tuberculosis Programme in India can be made more effective by applying operation research models. Similarly, Verma (1973) has recommended the application of such models in the 'field practice area' of the Medical College hospitals to increase the operational efficiency of health units of the area.

2.4 CONCLUSIONS.

In different areas of medicine and health, mathematical models are of profound significance. However, models developed so far are based mainly on deterministic approach. Those based on probabilistic laws/stochastic approach are very few. Moreover, available models are, by and large, computer-based, having been formulated mainly by the workers of developed countries; depending upon their resources

and disease patterns. Some models, therefore, are not of much use in developing countries like ours, either because the epidemiologic behaviour of the diseases and their patterns here are relatively different or the computer facilities are not in abundance. Attempts should be made to formulate simple models, particularly those based on probabilistic/stochastic approach, taking resources and conditions of the developing countries like ours into account.

Further, there are many problems in assessing any model for its general applicability. Lack of adequate data forms major difficulty in this regard. Thus, there is a need to undertake surveys to make relevant data available. Such data can be obtained from control projects for which careful evaluations are planned. After a phase of base line data collection, the model can be fitted to the local situations; projections of likely intervention effects can be made and later compared with the actual observations. The success would, however, depend upon the close cooperation between epidemiologists and model builders (Dietz, 1977).

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CHAPTER III

BRIEF EPIDEMIOLOGY OF MALARIA AND MALARIA MODELS

BRIEF EPIDEMIOLOGY OF MALARIA AND MALARIA MODELS

Malaria, in India, is a major public health problem. The disease causes high morbidity with a considerable load of mortality. Before the National Malaria Control Programme (N.M.C.P.) was undertaken in the country, it was estimated that '75 million people suffered from malaria and about 8 lakhs died directly due to it in normal years. However, in epidemic years, this number would almost double' (Government of India, 1976). Encouraged by the results achieved in the Programme (N.M.C.P.), Government switched over to the National Malaria Eradication Programme (N.M.E.P.) in the year 1958. The load of positive cases of malaria was drastically reduced from 75 million per year to about 1 lakh per year in 1965.

The Programme (N.M.E.P.), however, began to have set backs after 1965 due to various reasons. Some of the important ones were - (i) insecticide sprays could not be carried-out according to schedule in view of delayed receipt of imported insecticides following the closure of Suez Canal in 1965,

(ii) malaria mosquitoe developed resistance to D.D.T., thus, necessitating alternate insecticides like B.H.C. and Malathion which are costlier and needed in greater quantity for effective use, (iii) cost of insecticides went up tremendously after the oil crisis, and (iv) people's co-operation in accepting insecticidal spray decreased.

In recent years, despite the continuous antimalaria efforts of the Government, country has shown increasing incidence with time. In order to check this malady, a greater attention of health professionals, especially of epidemiologists and of health statisticians looks to be an urgent need.

Malaria situations in the communities are usually measured with the help of simple statistical indices. The indices, such as - sple n rate, parasite rate, infant parasite rate, proportional case rate, annual parasite index (A.P.I.), annual blood examination rate (A.B.E.R.), cause specific death rate and recovery rate etc are, thus, in use. However, the phenomena of the disease have not been studied utilizing random concepts hitherto. There is, thus, a need to investigate the mechanism of various epidemiological aspects of malaria using stochastic approaches.

3.1 CONCEPT OF MALARIA EPIDEMIOLOGY

Malaria is a communicable disease caused by sporozoan parasites of the genus Plasmodium and transmitted to man by certain species of infected, female Anopheline mosquitoes. The disease is characterized clinically by periodic chills and fever, enlargement of spleen and secondary anaemia with a tendency to relapses.

(I) Agent

Malaria in man is caused by 4 species of the malaria parasites - P.vivax, P.falciparum, P.malariae and P.ovale. Of these, P.vivax has the widest distribution throughout the world. In India, 65-69% of the infections are reported to be due to P.vivax; 25-30% due to P.falciparum and 4-8% due to mixed infections (Park and Park, 1977). P.malariae has a restricted distribution and is said to be responsible for less than 1% of the infections in India. P.ovale is a very rare parasite of man; it is mainly confined to tropical Africa and Vietnam (W.H.O., 1970).

(II) Life history

Malaria parasite undergoes two cycles of development - the human cycle (asexual cycle) and the

mosquitoe cycle (sexual cycle). Man is the intermediate host and the mosquitoe is definitive host. The asexual cycle begins when an infected mosquitoe bites a person and injects the sporozoites. The sexual cycle is initiated when an Anopheline mosquitoe capable of transmitting malaria (vector) feeds on a malaria patient. The asexual forms of the parasite disintegrate in the stomach of mosquitoe while the sexual forms continue further development.

(III) Reservoir of infection

A person who harbours the sexual forms (gametocytes) of the parasite is the reservoir of infection. Certain conditions are, however, required to be fulfilled before a person can serve as a reservoir : (i) he must harbour gametocytes of both the sexes in his blood, (ii) the gametocytes must be mature; immature forms do not undergo further development, (iii) gametocytes must be viable in the sense that if the patient receives an antimalaria drug, the gametocytes lose their viability or infectivity to mosquitoes and, (iv) the gametocytes must be present in sufficient density to infect mosquitoes.

(IV) Period of communicability

Malaria is communicable as long as mature and viable gametocytes exist in the circulating blood in sufficient density to infect mosquitoes. In vivax infections, gametocytes appear in blood 4-5 days after the appearance of asexual parasites; in falciparum infections, they do not appear until 10-12 days after the first appearance of asexual parasites. Further, it is usual for vivax and ovale malaria to relapse more than 3 years after the patient's first attack. Recurrences of falciparum malaria usually disappear within 1-2 years. P.malariae has a tendency to cause prolonged low level, asymptomatic parasitaemia. This infection is known to persist for more than 30 days.

(V) Mode of transmission

Malaria is transmitted by the bites of certain species of infected, female, Anopheline mosquitoes. The mosquitoe is not infected unless the sporozoites are present in the salivary glands. In nutshell, the conditions necessary for the transmission of malaria are : (i) a reservoir of infection, i.e., the presence of individuals with the sufficient number of mature viable, male and female gametocytes in their

blood, (ii) the presence of sufficient number of atleast one species of Anopheline mosquitoe which is capable of transmitting malaria, (iii) favourable climatic conditions for the development of sexual cycle in the insect-vector to live long enough to allow the sexual cycle to be completed, (iv) the presence of susceptible human beings to whom the infection may be transmitted.

Apart from mosquitoe bite, malaria may be transmitted by blood transfusion (Brue-Chwatt, 1974). In drug addicts, it may also be transmitted by shared syringes (Hall, 1976; British Medical Journal, 1976).

(VI) Incubation period

A certain period of time usually lapses between the entry of disease agent and onset of clinical signs and symptoms in the patient. This period is known as incubation period.

In malaria, the length of time (incubation period) between the bite of an infected mosquitoe and the first attack of fever is usually not less than 10 days. This period may, however, vary according to the species of parasite. Usually, about 12 days are required for the development of P.falciparum infection,

13-15 days for P.vivax and P.ovale, and upto one month for P.malariae infection.

(VII) Treatment

Three sorts of treatment - presumptive, radical and mass drug therapy for controlling the disease in the communities are generally used in malaria. Presumptive treatment is based on the assumption that every fever case is due to malaria unless proved otherwise. On this assumption, a single dose of 4 chloroquine tablets (600 mg.) for an adult, and proportionate doses for children, is administered to all fever cases.

If the blood slide is positive for malaria parasite, radical treatment is given. In India, the standard treatment is based on a 5-day regimen of chloroquine in combination with primaquin. Under revised strategy, mass drug therapy has also been recommended in areas where annual parasite index (A.P.I.) is between 5-10 cases per 1,000 population.

3.2 MALARIA MODELS SO FAR.

Shortly after Anophelines were shown to carry malaria by Sir Ronold Ross, many studies on different aspects, viz., immunology, entomology and epidemiology

of malaria were carried-out in different parts of the world. A few quantitative studies on the subject (Ross, 1911; MacDonald, 1950; 1952 and Rao et al, 1976) are also available. However, the literature dealing with the development of mathematical models and their applications to the various aspects of malariology is considerably deficient. Some available models of malaria are indicated, in brief, here.

Ross (1911) evolved a model to examine the apparent correlation found between the number of Anopheline mosquitoes and infected persons in a locality. MacDonald (1950) assumed that the happenings should also include the effect of superinfection and thus, extended the basic theory of Sir Ronald Ross. MacDonald (1957) later developed a mathematical theory of the transmission dynamics of malaria by assuming that mosquitoe population is stationary and that, proportion of bites on man which are infective to the mosquitoes is the same as the proportion of human population affected. A stochastic model, assuming that the resultant effect of factors influencing the spread of disease from one generation to the other be regarded as a random process has also been formulated (MacDonald et al, 1968).

Najera (1974), however, broughtforth many lacunae in the MacDonald (1957) model of malaria epidemiology. He applied MacDonald's model to the data collected in a W.H.O. Malaria Control Field Research Trial in an area of northern Nigeria and found that observed results were in great variance with those predicted by the model. He, inter alia, concluded that MacDonald's model represents epidemiological knowledge of 1950. It is heavily overloaded with the entomological variables and many relevant parasitological variables have not been taken into account. Thus, this model might fail to measure precisely the epidemiological situations of the disease in a population in respect of many variables under present developing knowledge of malaria epidemiology.

Pull and Grab (1974) applied simple and reversible catalytic models of Muench (1959) for studying incidence and prevalence rates of malaria parasites in infants. They found these models to be fit to predict malaria-rates in infants satisfactorily, considering constant risks of infection and of recovery.

Dietz et al (1974) developed a computer-simulation model considering deterministic approach

and tested its applicability and suitability in African Savanah. The model defines 7 transition states of the dynamics of malaria and consists of a set of mathematical equations, simultaneous solution of which provides values to many parameters desired. A similar type of computer-simulation model based on stochastic approach has been constructed by Rao et al (1976). The model has been used in P.vivax epidemiology considering arbitrary values to different parameters available in the literature.

3.3 LACUNAE IN AVAILABLE MALARIA MODELS.

It may, thus, be seen that only a few studies on malaria are available where mathematical models, based on stochastic processes, have been applied. Not only this, the available models, in general, are so complicated that their use seems difficult where computer facilities are not available. With recrudescence of malaria in some countries including India, the patterns of disease need be studied taking present epidemiological knowledge of the disease into account. The use of random processes in studying epidemiological patterns of the disease is important as the assumptions of the deterministic systems that, with a given set of initial conditions, only a single sequence of events will ensue, may lead to unrealistic

conclusions. Further, during disease generation, variety of factors may intervene to alter the spread of disease to the potential victims of next generation.

Thus, there seems to be a need to develop simple stochastic models and apply them for studying epidemiological patterns of the disease. Such models would enable one to study malaria situations at micro as well as macro levels easily, particularly in those situations where facilities of compters are not in abundance.

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CHAPTER IV

ESTIMATION OF MALARIA PARASITE INCIDENCE RATES IN INFANTS FROM LONGITUDINAL DATA

ESTIMATION OF MALARIA PARASITE INCIDENCE RATES IN INFANTS FROM LONGITUDINAL DATA

The planning of preventive measures against communicable diseases requires both – a good knowledge of natural course of these diseases and reliable information on the actual values of main factors involved in the transmission processes. For a disease like malaria, study of its quantitative aspects, such as – transmission of infection from vector to the man etc is essential. Assessment of malaria situations in a region on such an aspect is generally made by estimating malaria parasite incidence rate in infants who are considered to be negative for malaria (i.e. free from malaria parasites) at birth. Here, the two methods – one based on Stochastic approach and the other based on Life Table approach – are illustrated to estimate such rates in infants.

4.1 STOCHASTIC APPROACH.

The longitudinal studies on malaria in infants are commonly used to estimate the incidence rate of the disease. The newborns, however, contract the infection

as they grow old and come in the contact with the disease agent. In holoendemic and hyperendemic areas, the estimation of 'force of infection' acting on the population of an area or rate of 'effective contacts' where 'effective contact' is defined to mean contact with aetiologic agent of sufficient intensity to cause infection in a nonimmune individual, can well be done by measuring rate of disease acquisition. It would, however, require follow-up of large number of new-borns. A simple stochastic model for estimating infective force of malaria and its age specific incidence rates in infants is formulated considering a few assumptions.

4.1.1 ASSUMPTIONS.

Let a cohort of infants be studied for presence or otherwise of malaria parasites in their blood longitudinally. Supposing that infants' experience with the disease agent can be recorded, we make following assumptions.

(i) Each infant of the cohort is susceptible to the malaria infection at birth.

(ii) Infants are equally likely to contact the disease agent and to respond to such contact in any given manner. Such assumption clearly implies that all

genetic and cultural subgroups within the cohort are equally susceptible to the infection.

(iii) Acquisition of infection by one infant of the cohort at any point of time does not influence the probability of infection by the other. Further, consideration is given to the cohort which is embeded in the larger population to the assumption that disease agents are constantly present in the environment.

(iv) The members of the cohort are exposed to a constant force of infection. This is, in fact, a gross over simplification of a complex set of factors. However, under stable* malaria conditions, this assumption is quite reasonable.

(v) The constant force of infection or risk of getting parasitaemia can directly be measured in terms of effective contacts per susceptible infant per unit of time, no matter how complex the events leading to these contacts may be; and that the evidence of effective contacts is provided by blood smear positivity for malaria parasites.

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* Under stable malaria conditions, the variations in the human parasite reservoir are small and their role in the transmission of parasites can easily be neglected.

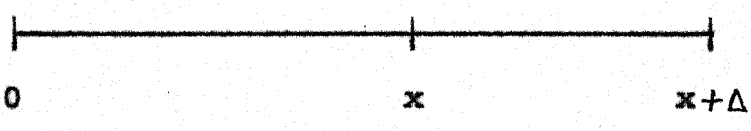
In fact, the above assumptions represent a deliberate simplification of the complex factors involved in the epidemiology of malaria.

4.1.2 THE MODEL.

Suppose the newborns are examined for presence or otherwise of malaria parasites in the blood by conducting follow-up surveys at suitable intervals. Since, the infants who are free from parasitaemia at age $x = 0$ where x is measured in terms of days, will get primary infection after certain life-span (or age), we denote this continuous period of age prior to the infection by a random variable x. Let 'a' be the constant instantaneous force of infection and for every infant, the probability of effective contact in a small time interval of length Δ be a Δ. Now considering distribution function of age at infection,

$$F_X(x) = P(X \leq x)$$

= Probability that an infant would meet a primary infection prior to or at age x.



Now, consider interval $(0, x + \Delta)$ and corresponding distribution function. Further, for a newborn to be infected for the first time at or before age $x + \Delta$, he must either be infected before age x or be free from infection within the interval (0, x) and be infected in the interval $(x, x + \Delta)$. Therefore,

$$F_X(x + \Delta) = F_X(x) + [1 - F_X(x)] \; [a\Delta + 0(\Delta)] \qquad \text{----------(1)}$$

where 'a' is the force of infection in terms of 'effective contacts' per susceptible infant per unit of time and $a\Delta + 0(\Delta)$ is the probability that an infant free from infection at age x is infected in the interval $(x, x + \Delta)$. Therefore, rearranging (1), we get,

$$\frac{F_X(x + \Delta) - F_X(x)}{\Delta} = a[1 - F_X(x)] + \frac{0(\Delta)}{\Delta}$$

Taking limit and letting $\Delta \to 0$, we have the differential equation,

$$\frac{d}{dx} F_X(x) = a[1 - F_X(x)]$$

$$\int_0^x \frac{dF_X(x)}{1 - F_X(x)} = \int_0^x a \, dx + C, \quad \text{where C is a constant.}$$

Or,

$$\text{Log}\,[1 - F_X(x)] = -ax + C$$

Applying initial conditions,

$F_X(0) = 0$ when $x = 0$ and thus, $C = 0$.

Therefore,

$$1 - F_X(x) = e^{-ax}$$

or,

$$F_X(x) = 1 - e^{-ax} \quad \text{----------(2)}$$

Here, for known value of 'a', values of $F_X(x)$ can be worked-out for different x's from (2) easily. Thus, function $F_X(x)$ will estimate cumulative age specific malaria parasite incidence rate in the population.

The p.d.f. of x will be,

$$\frac{d}{dx} F_X(x) = f_X(x) = a\, e^{-ax}, \quad x \geq 0$$
$$= 0 \qquad\qquad x < 0 \quad \text{------(3)}$$

The mean age at primary infection will be,

$$E(x) = \int_0^x x\, f_X(x)\, dx$$

$$= a \int_0^x x\, e^{-ax}\, dx$$

on integrating by parts,

$$E(x) = \frac{1}{a} \quad \text{----------(4)}$$

4.1.3 ESTIMATION OF PARAMETER.

Suppose that following set of data is given for a cohort of N_o newborns.

x_i : Age at primary infection or the mid-point associated with the ith age-interval.

s_x : Number of susceptible infants who could remain un-infected at the end of the follow-up.

T_{x_i} : Number of primary infections within the ith age-interval.

W_{x_i} : Number of withdrawals without being infected in the ith interval due to closure of the study.

Then, parameter 'a' can easily be estimated by the method of maximum likelihood as follows.

Here, the probability that an infant who withdraws is not infected to age xi is $e^{-a x_i}$; the probability density that an infant is infected at age x_i is a $e^{-a x_i}$ and that he is not infected during entire period (0, x) of observation, i.e., till closure of the study is $p_x = e^{-a}$.

The maximum likelihood function for given s_x, T_{x_i}, W_{x_i} will be

$$L = \prod_{i=1}\left[(p_x)^{s_x} \quad (ae^{-a\,x_i})^{T_{x_i}} \; (e^{-a\,x_i})^{W_{x_i}}\right]$$

$$= (e^{-a})^{s_x} \prod_{i=1}\left[(ae^{-a\,x_i})^{T_{x_i}} \; (e^{-a\,x_i})^{W_{x_i}}\right]$$

$$\text{Log } L = -a\,s_x + \sum_{i=1} T_{x_i} \log a - \sum_{i=1} a\,x_i\,T_{x_i} - \sum_{i=1} a\,x_i\,W_{x_i}$$

Differentiating with respect to 'a' and putting $\frac{\partial}{\partial a} \log L = 0$

We get,

$$\sum_{i=1} T_{x_i} \Big/ a = s_x + \sum_{i=1} x_i\,T_{x_i} + \sum_{i=1} x_i\,W_{x_i}$$

$$\text{Thus, } \hat{a} = \frac{\sum_{i=1} T_{x_i}}{s_x + \sum_{i=1} x_i\,T_{x_i} + \sum_{i=1} x_i\,W_{x_i}} \qquad \text{----------(5)}$$

Putting $\sum_{i=1} T_{x_i} = T_x$ in (5), we have

$$\hat{a} = \frac{T_x}{s_x + \sum_{i=1} x_i\,T_{x_i} + \sum_{i=1} x_i\,W_{x_i}} \qquad \text{----------(6)}$$

Thus, the maximum likelihood estimate of intensity of risk or force of infection 'a' of malaria acting on the population under observation is equal to the number of

infections, occurring during the period of observation (0, x) divided by total length of un-infected age, enjoyed by the N_o newborns during the entire period of observation.

4.1.4 APPLICATION OF MODEL TO THE NUMERICAL DATA.

Application of the model for estimating incidence rates in infants would require data on primary infection of malaria in them. Such data can be obtained only by undertaking longitudinal studies on a group of newborns and then examining their blood for presence or otherwise of malaria infection at suitable intervals. In India, because of many obvious difficulties in such studies, proper data on primary infections in infants are not available for any part of the country. In such circumstances, the model was applied to the parasitological data, gathered in a W.H.O. Field Trial (Pull and Grab, 1974) of a new insecticide in Kenya, shown in Table 4.1. Some details showing calculation of force of malaria infection 'a' acting on the population of that area have also been given in Table 4.1.

Here, value of 'a', the daily force of infection of malaria, worked-out from (6) is 0.0069.

TABLE 4.1

Age-specific malaria parasite incidence rates and calculation of the 'force of infection' in infants by utilizing a stochastic model in a population of Kenya#.

Age (Months) Interval	Mid-point (x_i)	No.of susceptible infants studied (N_{x_i})	No.of primary infections (T_{x_i})	No. of with-drawals*	Monthly parasite incidence rate (%)	$x_i T_{x_i}$	$x_i W_{x_i}$
0 - 1	0.5	507	12	52	2.4	6.0	26.0
1 - 2	1.5	443	82	41	18.5	123.0	61.5
2 - 3	2.5	320	73	25	22.8	182.5	62.5
3 - 4	3.5	222	64	27	28.8	224.0	94.5
4 - 5	4.5	131	33	19	25.2	148.5	85.5
5 - 6	5.5	79	26	14	32.9	143.0	77.0
6 - 7	6.5	39	11	7	28.2	71.5	45.5
7 - 8	7.5	21	5	0	23.8	37.5	0.0
8 - 9	8.5	16	3	7	18.8	25.5	59.5
9 - 10	9.5	6	1	1	16.7	9.5	9.5
Total		$\$_x = 4$	310	193	-	971.0	521.5

Source : Pull and Grab (1974).

* Also includes dead and cases 'lost to follow up', if any.

This indicates that 69 infants got fresh malaria infection daily for every 10,000 population of newborns. The mean age of the acquisition of the disease is calculated to be 4.83 months, indicating that all infants in the studied population were infected from malaria by an average age of 4.83 months.

The source of data unfortunately, did not reveal details on number of infants who were dead and/or 'lost to follow up' at different ages. Thus, column fifth of Table 4.1, showing withdrawals at different ages also includes cases dead or those'lost to follow up', if any. In such a situation the exact estimation of 'a' from the formula (6) is, indeed, not possible. The calculated value of 'a' (i.e. 0.0069) would, thus, be an under-estimate of the infective force and may, therefore, adversely affect the fitness of model to the observed data.

The age-specific cumulated rates of new malaria cases were derived from observed age-specific monthly parasite incidence rates (shown in Table 4.1) in an initial cohort of 10,000 newborns (Table 4.2). Table 4.2 also depicts comparative study of observed and expected monthly parasite incidence rates, estimated from the model formulated.

TABLE 4.2

Observed and expected age-specific cumulated malaria parasite incidence rates based on stochastic model in a cohort of 10,000 new-borns.

Age in days (x)	Observed monthly parasite incidence rate (%)	Size of the cohort	NO. OF NEW MALARIA CASES IN COHORT		ax	$1-e^{-ax}$	AGE SPECIFIC CUMULATED RATE	
			Per month	Cumulated			Observed (%)	Expected (%)
0		10,000						
30	2.4	9,760	240	240	0.207	0.1869	4.8*	18.7
60	18.5	7,950	1,810	2,050	0.414	0.3389	20.5	33.9
90	22.8	6,140	1,810	3,860	0.621	0.4625	38.6	46.3
120	28.8	4,370	1,770	5,630	0.828	0.5630	56.3	56.3
150	25.2	3,270	1,100	6,730	1.035	0.6447	67.3	64.5
180	32.9	2,190	1,080	7,810	1.242	0.7112	78.1	71.1
210	28.2	1,570	620	8,430	1.449	0.7652	84.3	76.5
240	23.2	1,200	370	8,800	1.656	0.8091	88.0	80.9
270	18.8	970	230	9,030	1.863	0.8450	90.3	84.5
300	16.7	870	160	9,190	2.070	0.8738	91.9	87.4

* Rate adjusted on the assumption of 15-day incubation period.

OBSERVED AND EXPECTED COMULATIVE MALARIA PARASITE INCIDENCE RATES(%),ESTIMATED BY STOCHASTIC MODEL IN INFANTS BY AGE.

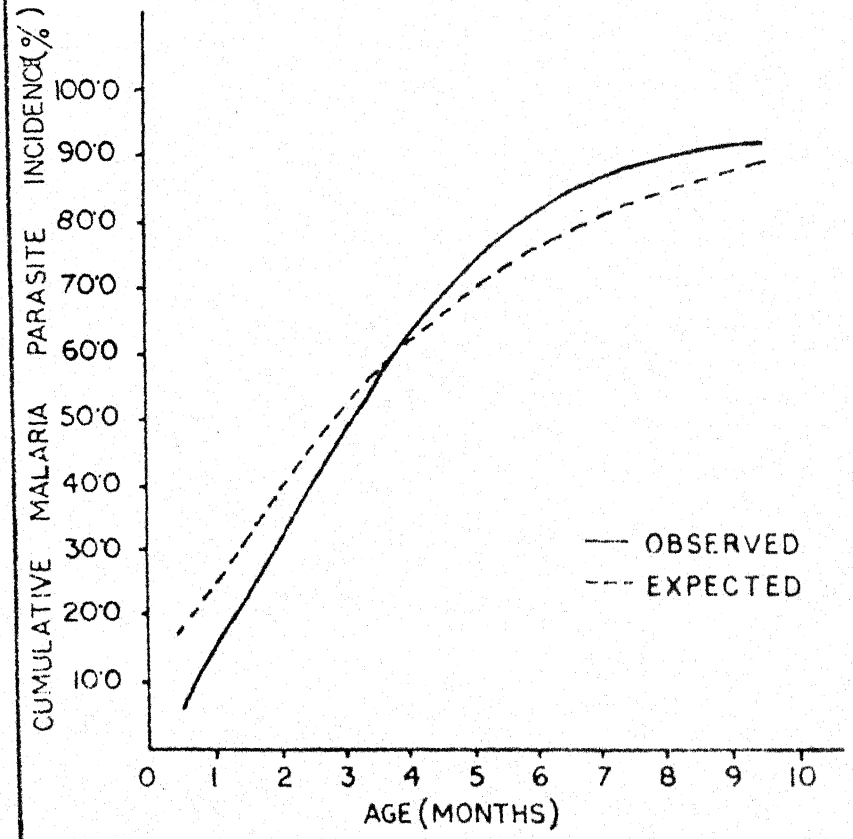


FIGURE 4·1

Curves on observed and theoretical age-specific malaria incidence rates have been shown in Figure 4.1. These curves, by and large, do not show much deviations; the trend of both the curves being closely similar. The model may, thus, be taken to simulate actual observations, more or less, satisfactorily.

The model, however, seems to over-estimate and underestimate malaria parasite incidence rates at early and late ages respectively. Such observations indicate that our assumption of constant force of infection, acting on the population is not quite appropriate. The lower risk of acquiring infection observed in the first month of age is probably due to lengthening of pre-patent period by maternal antibodies. Further, observed deviations, to some extent, in parasite incidence rates, might have also been contributed by the possible under-estimation in the infective force of malaria. It is, however, thought that the formulated model would provide better fit to the observed malaria situations if the appropriate data with relevant details are available.

4.2 LIFE TABLE APPROACH.

Long before the development of modern probability and statistics, people were concerned with the length of life and they constructed tables to measure longevity. Life Tables are generally designed to study the mortality experience of a group of people from birth until last person dies. Although, such tables are the product of actuarial science, their application, which was previously considered somewhat limited, is now increasing considerably with time. Advances in the theoretical statistics and stochastic processes have made it possible to study length of life from purely a statistical point of view, making Life Table a valuable analytical tool for demographers, epidemiologists and for many others (Chiang, 1968). Here, an attempt has been made to illustrate the application of such a table for estimating malaria parasite incidence rate in an infant population.

4.2.1 METHODOLOGY.

In order to use Life Table methodology for the present purpose, its general concept will have to be slightly modified.

(I) General

Let there be a group of newborns who are free from malaria at the time of their birth but susceptible to such infection afterwards. Newborns are studied longitudinally for malaria parasites in their blood for specified period of time from a well defined zero point. When the time of observation ends, it is seen that morbidity data on malaria for certain infants are incomplete. Various factors contribute to this incomplete data: some infants, at end of the study generally remain un-infected; some of them die in view of high infant mortality rate, particularly in developing countries like India, from the causes other than malaria; and a few are 'lost to follow up' because of many likely reasons. These sources of incomplete information must be taken into consideration while estimating malaria parasite incidence rate using Life Table methodology.

For present purpose, a group of newborns under observation is regarded as one large cohort, beginning with age $x = 0$, where x is measured in terms of months. Therefore, the number of infants who contribute to the first month of life are those who had entered in the study during the entire period considered, for example,

say, 13 months. The number contributing to the second month of life consists of those followed-up for at least one month or those who had entered the study during the first 11 months of the year. Those who entered the study in the last month of the year are due for withdrawal in the analysis in the first month and those who entered the study in the month prior to the last month are due for withdrawal in the second month etc.

Furthermore, every newborn included in the study is subject to the risk of being 'lost' or dead and only a few of them would be withdrawn in any class-interval. Consequently, 'lost' and withdrawals belong to two different categories and can not be treated equally while calculating incidence rate of the disease. Thus, the 'lost' cases in such studies should be considered as one of the risks competing with the risk of disease.

(II) Notations and definitions

Various Life Table functions which may be adapted and used here are defined below.

x : Age of the infant in month; $(x, x + n)$ is the age-interval taken into consideration, here $n = 1$.

l_x : Number of infants entering in the study at age x.

n^Tx : Number of primary infections of malaria during age interval (x, x + n).

n^Wx : Number of withdrawals in the interval (x, x + n).

l'_x : Effective number of infants exposed to the risk of malaria infection. In the studies like present one, intervals considered are usually short (here, it is of one month only). The infection rate may, thus, be considered to be uniformly distributed over intervals. It may further be assumed that infants withdrawn contribute, on an average, only half of the interval to the study. The effective number at the risk of malaria infection at age x would, therefore, be the number at the beginning of interval (x, x + n) less one half of the number seen at the end of this interval.

Or, $l'_x = l_x - (n^Wx)/2.$

n^qx : Probability that an infant aged x will be infected from malaria before reaching age (x + n)

Or, $n^qx = n^Tx/l'_x.$

$n^{p}x$: $1 - n^{q}x$. This is the proportion of un-infected infants at the end of the interval $(x, x + n)$.

P_x : Cumulative probability of an infant being free from malaria from birth through the interval $(x, x + n)$.

Or, $P_x = n^{p}o.\ n^{p}1.\ n^{p}2 \ldots\ldots\ n^{p}x - 1.$

Q_x : $1-P_x$

Here, the percentage value of cumulative probability function Q_x would provide cumulated malaria parasite incidence rates by age for infants.

The data, utilized here for the purpose of present illustration, have been derived from a longitudinal study, carried-out during preparatory phase of a W.H.O. Field Trial to test a new insecticide in Nyanza Province, Kenya (Pull and Grab, 1974).

4.2.2 APPLICATION OF LIFE TABLE METHODOLOGY TO THE NUMERICAL DATA.

The values of various parameters defined in (II) of Section 4.2.1 can either be seen directly from observed data or can be worked-out using formulae already illustrated in previous Sections. Table 4.3 shows values of various Life Table parameters, used here

TABLE 4.3

Application of Life Table Method to a cohort of 507 infants followed-up for first 10 months of life for the presence of malaria parasites[#].

Age (Months)	l_x	$_nT_x$	$_nW_x$*	l_x	$_nq_x$	$_np_x$	p_x	q_x
1	2	3	4	5	6	7	8	9
0 - 1	507	12	52	481.0	0.0250	0.9751	0.9751	0.0250
1 - 2	443	82	41	422.5	0.1941	0.8059	0.7858	0.2142
2 - 3	320	73	25	307.5	0.2374	0.7626	0.5993	0.4007
3 - 4	222	64	27	208.5	0.3070	0.6931	0.4153	0.5847
4 - 5	131	33	19	121.5	0.2716	0.7284	0.3025	0.6975
5 - 6	79	26	14	72.0	0.3611	0.6389	0.1933	0.8067
6 - 7	39	11	7	35.5	0.3099	0.1901	0.1334	0.8666
7 - 8	21	5	0	21.0	0.2381	0.7619	0.1016	0.8984
8 - 9	16	3	7	12.5	0.2400	0.7600	0.0772	0.9228
9 - 10	6	1	1	5.5	0.1818	0.8182	0.0632	0.9368

Columns 1 - 4 are based on the data obtained in a W.H.O. Project; for reference, see Pull and Grab (1974).

* Column 4 also includes dead or 'lost' cases, if any.

TABLE 4.4

Observed and expected cumulative malaria parasite incidence rate by age, based on Life Table Methodology and Stochastic Model in an infant population.

Age (Months)	MALARIA INCIDENCE RATE (%)		
	Observed	Expected Rate Based On	
		Life Table Method	Stochastic Model
0 - 1	4.8*	2.5	18.7
1 - 2	20.5	21.4	33.9
2 - 3	38.6	40.1	46.3
3 - 4	56.3	58.8	56.3
4 - 5	67.3	69.8	64.5
5 - 6	78.1	80.7	71.1
6 - 7	84.3	86.7	76.5
7 - 8	88.0	89.9	80.9
8 - 9	90.3	92.3	84.5
9 - 10	91.9	93.7	87.4

* Rate adjusted on the assumption of 15-day incubation period.

OBSERVED AND EXPECTED CUMULATIVE MALARIA PARASITE INCIDENCE RATES (%), ESTIMATED BY LIFE TABLE METHOD IN INFANTS BY AGE.

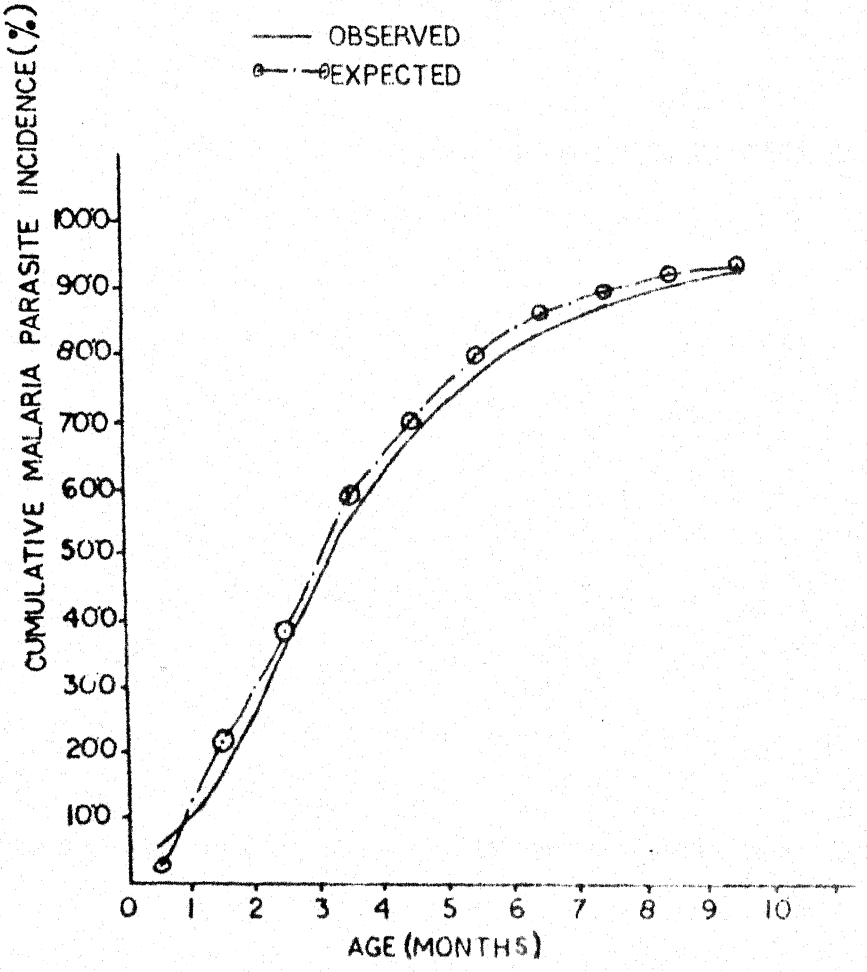


FIGURE 42

to estimate malaria parasite incidence rates. The actual comparison of the two rates - observed and expected - by age has been given in Table 4.4 as well as in Figure 4.2. It may be seen that estimates on cumulated malaria parasite incidence, based on Life Table Methodology are quite close to the observed data.

The observed rates and those estimated by Life Table Method are quite close to each other; however, some differences are visible at certain places. This is more apparent in case of extreme age-groups. The Life Table Method too under-estimates malaria parasite incidence rates in early age-groups and over-estimates in later ages. This could have been because of limitation of data available and used here. As outlined earlier, in the studies like present one, the informations on 'lost' cases and withdrawals should be dealt with separately for the calculation of values of different parameters. In the data, unfortunately, information on 'lost' cases was not available separately and was mixed with withdrawals. This might have contributed, to some extent, to such an observation. It is, however, thought that, had the appropriate details been available with data used here,

the Life Table Methodology would have estimated malaria parasite incidence rates more nearer to the observed data.

4.3 DISCUSSION ON THE TWO METHODS.

The estimation of malaria parasite incidence in infants has been a difficult problem since long. The two methods - Stochastic Model and Life Table Methodology - based on longitudinal data provide tools for estimating such rates. In spite of some limitations of data used in the illustration of the two methods for the purpose, both approaches - Stochastic Model and Life Table Method - measured the actual malaria situations quite satisfactorily.

The structure of the model, developed here is almost similar to the simple catalytic model of Muench (1959), evolved on the basis of deterministic approach. Estimation of parameters in Muench (1959) model requires lengthy calculations and a chart which he has developed for the purpose. The present model, on the other hand, is very simple to understand and feasible to apply. The estimation of only parameter 'a' from the observed data is also quite easy.

Comparative observations on age-specific malaria parasite incidence rates, estimated by the

COMPARISON OF ESTIMATED CUMULATIVE MALARIA PARASITE INCIDENCE RATES (%) BY TWO METHODS — STOCHASTIC MODEL AND LIFE TABLE METHOD VIS-A-VIS TO THE OBSERVED RATES.

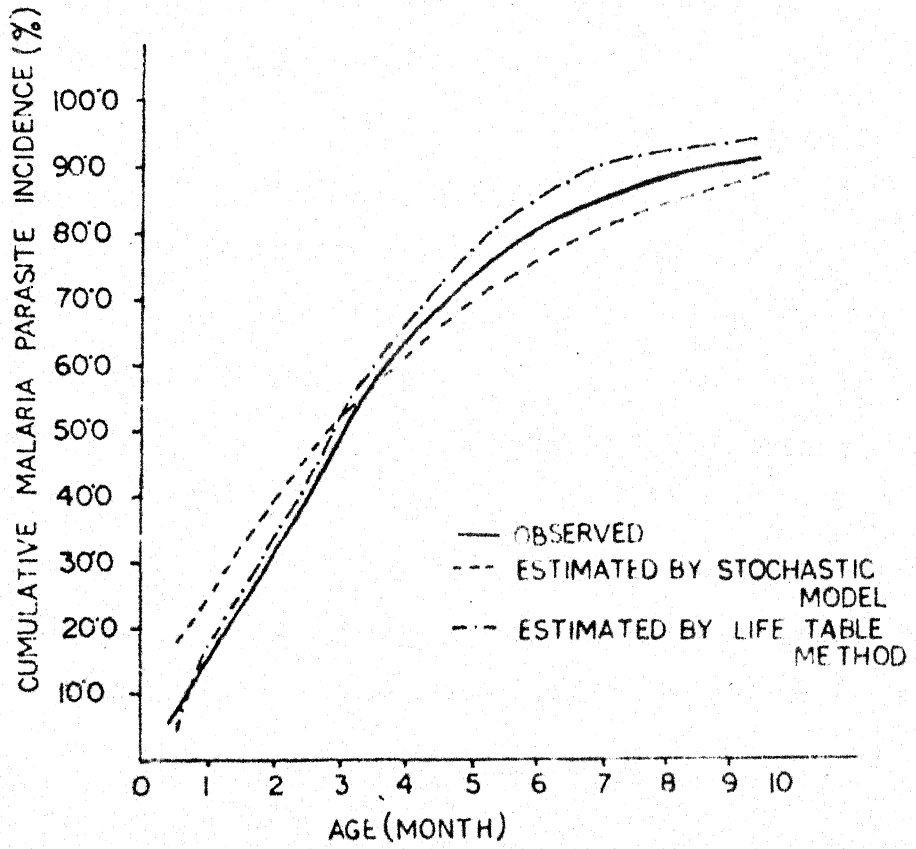


FIGURE 4·3

Stochastic Model and Life Table Method vis-a-vis the actual rates observed in the area can be made from Table 4.4 (Figure 4.3). Graphical presentation of data (Figure 4.3) reveals that model over-estimates such rates in early months and under-estimates in later months of their ages. The Life Table Method, on the other hand, estimates somewhat higher rates in every age-group except for those infants who are below 2 months of age. The rates, estimated by Life Table Method, however, seem to be relatively closer than those estimated by the model inspite of limitations of data used. This may be taken to be an indication that the considered assumption on constant 'force of infection' irrespective of age is not very appropriate. Furthermore, the limited details available with the data might have influenced results, based on model to a greater extent than that of Life Table case. Because of limitations of data, exact comparison of results is not possible. It is, however, pondered that both the methods would estimate observed parasite incidence rates by age more closely than those at present, in cases where data would provide all required details.

The selection of strategy for control/ eradication of malaria is generally based on the

expected effect of technically feasible intervention methods and their cost. A mathematical model of the epidemiology of malaria may rationalize this selection by allowing the quantitative comparisons of the relative effects of different intervention methods and their combinations. The present attempt may, therefore, be a significant contribution in this regard. Further, the methods suggested here may be used for describing actual epidemiological processes and for predicting the expected incidence of the disease in a non-immune population when variations occur in the force of infection - either under natural conditions or under the influence of control measures. They may also be used as a basis for estimating the degree of reduction in the 'force of infection' to be brought-about by intervention measures in order to achieve targets set in advance.

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CHAPTER V

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA – A STOCHASTIC MODEL CONSIDERING TWO STATES ONLY

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA — A STOCHASTIC MODEL CONSIDERING TWO STATES ONLY

Quantification of various epidemiological aspects of malariology is important for studying the extent of problem and evolving measures for its control at local as well as at national levels. Malaria parasite incidence, recovery rates and malaria transition probabilities are useful statistical parameters, frequently used in the quantitative studies on the epidemiology of the disease.

Malaria parasite incidence rate or human infection rate is defined as the rate at which 'negatives' are transferred to 'positives' via incubating state (Dietz et al, 1974). In other words, it is the daily mean number of bites inflicted on any individual by mosquitoes, infected with sporozoites which are actually infective (MacDonald, 1957). This gives the proportion of human population receiving infective inocula in a unit of time.

The recovery rate is defined (MacDonald, 1957) as the proportion of people affected from malaria who would revert to the free from malaria state in an unit of time. To be practical, affected group will be that showing parasitaemia at the time of examination of blood. As the termination is usually gradual with increasing intervals of freedom from parasitaemia (Pampana, 1969), the recovery rate represents the increasing probability of being free from parasitaemia when examined.

Incidence and recovery rates of the diseases are estimated by conducting longitudinal studies. In malaria, such rates can be estimated by studying a homogeneous group of population for the presence of malaria parasites in the blood by conducting follow-ups at suitable intervals. An assumption will, however, have to be made that, between two consecutive surveys, only one type of transition - from 'negative'to 'positive' in first case, and from 'positive' to 'negative' in the second case - is possible.

Here, an attempt is made to suggest a Stochastic Model with only two states for estimating daily malaria parasite incidence and recovery rates from longitudinal data. Formulation of the model is

based on the assumption that sampled individuals, studied initially are covered, in toto, during subsequent follow-ups.

5.1 ASSUMPTIONS.

Let a population, homogeneous in nature, be followed-up at suitable intervals and cases of malaria be detected at each survey with a standard method of blood examination. Following assumptions are made.

(i) Individuals of the population are at risk to suffer from malaria during the period of their observation.

(ii) At any point of time during a given period, individuals can have only two states – S_1 and S_2, S_1 being parasite negative state or simply 'negative' state and S_2 being parasite positive state or simply 'positive' state.

(iii) Individuals' transitions from one state to the other are independent of their past transitions, if any and, they are transferred at a constant rate from one state to the other.

(iv) The probability of making one transition – from negative to positive or vice-versa – in a single

FLOW CHART OF A MALARIA MODEL CONSIDERING ONLY TWO STATES-SHOWING POSTULATED NUMBER OF STATES AND POSSIBILITIES OF TRANSITIONS.

S.NO.	STATE	CONSIDERED TIME INTERVAL 0.....τ.....t
1.	FREE FROM MALARIA	S_1 → S_1
2.	POSITIVE FOR MALARIA	S_2 → S_2

FIGURE-5.

unit of time is very small and that probability of making more than one transition in a unit of time is negligible.

(v) All individuals, studied initially for malaria are covered, in toto, during subsequent follow-ups.

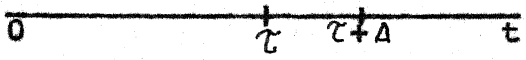
5.2 THE MODEL.

According to the results of blood examination, individuals of the population can well be categorized each time in one of the two defined states - S_1 and S_2. Without loss of generality, the time point at the first observation can be taken as zero and at subsequent observations as t, t being measured in terms of days. Individuals, during the period (0, t) will travel continuously from state S_i to S_j, for i, j = 1, 2 (Figure 5.1). Individuals' transitions between the states would be governed by respective intensities of risks, defined as follows.

State S_i	State S_j	
	S_1	S_2
S_1	-a	a
S_2	b	-b

----------(1)

The probabilities of transitions from state S_i to S_j at any point of time τ , for $0 \leq \tau \leq t$ may be defined as,



P [Individual in state S_1 at time τ will be in state S_2 at time $\tau + \Delta$] $= a\Delta + 0(\Delta)$

P [Individual in state S_2 at time τ will be in state S_1 at time $\tau + \Delta$] $= b\Delta + 0(\Delta)$

P [Individual in state S_1 at time τ will remain in same state at time $\tau + \Delta$] $= 1 - a\Delta - 0(\Delta)$

P [Individual in state S_2 at time τ will remain in same state at time $\tau + \Delta$] $= 1 - b\Delta - 0(\Delta)$

An individual in state S_i at $t = 0$ may be in any one of the S_j states at time t; the corresponding probabilities $P_{ij}(t)$ will satisfy following initial conditions.

$$P_{ij}(0) = 0, \text{ for } i = j$$
$$= 1, \text{ for } i \neq j \qquad \text{----------(2)}$$

Considering contiguous time intervals (0, t) and (t, $t + \Delta$), the differential equations are obtained as,

$$
\begin{aligned}
P_{11}(t+\Delta) &= P_{11}(t)(1-a\Delta) + P_{12}(t)\, b\Delta + 0(\Delta) \\
P_{12}(t+\Delta) &= P_{11}(t)\, a\Delta + P_{12}(t)(1-b\Delta) + 0(\Delta) \\
P_{21}(t+\Delta) &= P_{21}(t)(1-a\Delta) + P_{22}(t)\, b\Delta + 0(\Delta) \\
P_{22}(t+\Delta) &= P_{21}(t)\, a\Delta + P_{22}(t)(1-b\Delta) + 0(\Delta)
\end{aligned}
\qquad \text{----(3)}
$$

Rearranging equations given in (3) and taking limit as $\Delta \longrightarrow 0$, we have

$$
\begin{aligned}
\frac{\partial}{\partial t} P_{11}(t) &= -a\, P_{11}(t) + b\, P_{12}(t) \\
\frac{\partial}{\partial t} P_{12}(t) &= a\, P_{11}(t) - b\, P_{12}(t) \\
\frac{\partial}{\partial t} P_{21}(t) &= -a\, P_{21}(t) + b\, P_{22}(t) \\
\frac{\partial}{\partial t} P_{22}(t) &= a\, P_{21}(t) - b\, P_{22}(t)
\end{aligned}
\qquad \text{--------(4)}
$$

Equations (4) are linear first order differential equations with constant coefficients and may, thus, have solution of the form

$$P_{ij}(t) = C_{ij}\, e^{rt}, \text{ for } i, j = 1, 2 \qquad \text{--------(5)}$$

Substituting (5) in (4) and rewriting them gives,

$$
\begin{aligned}
C_{11}(r + a) - C_{12}\, b &= 0 \\
C_{12}(r + b) - C_{11}\, a &= 0
\end{aligned}
\qquad \text{----------(6)}
$$

and

$$\left.\begin{aligned} C_{21}(r + a) - C_{22}\, b &= 0 \\ C_{22}(r + b) - C_{21}\, a &= 0 \end{aligned}\right\} \quad \text{----------(7)}$$

Since (6) and (7) are the linear systems, the non-trival solutions of C_{ij}'s would exist only if the determinant

$$\begin{vmatrix} (r + a) & -b \\ -a & (r + b) \end{vmatrix} = 0 \quad \text{----------(8)}$$

Solution of (8) gives two values of r, denoted by r_1 and r_2 here as follows,

$$r_1 = 0 \text{ and } r_2 = -(a + b).$$

It may be seen that in (6) and (7), coefficients C_{ij} corresponding to each value of r_k (for k = 1, 2) are related as follows.

$$\frac{C_{11k}}{C_{12k}} = \frac{r_{k+b}}{a} = \frac{b}{r_{k+a}} = A_k \text{ (say)}$$

and

$$\frac{C_{22k}}{C_{21k}} = \frac{r_{k+a}}{b} = \frac{a}{r_{k+b}} = B_k \text{ (say)}$$

Rearranging and putting the value of C_{ijk} in (5), the values of two constants A_k and B_k are worked-out as

$$A_1 = \frac{1}{(a+b)} \quad , \quad A_2 = \frac{a}{b(a+b)}$$

and

$$B_1 = \frac{1}{(a+b)} \quad , \quad B_2 = \frac{b}{a(a+b)} \qquad \text{----------(9)}$$

Using (9) in (5), we finally obtain transition probabilities $P_{ij}(t)$ as follows.

$$\begin{aligned}
P_{11}(t) &= \frac{b}{a+b} + \frac{a}{a+b} e^{-(a+b)t} \\
P_{12}(t) &= \frac{a}{a+b} - \frac{a}{a+b} e^{-(a+b)t} \\
P_{21}(t) &= \frac{b}{a+b} - \frac{b}{a+b} e^{-(a+b)t} \\
P_{22}(t) &= \frac{a}{a+b} + \frac{b}{a+b} e^{-(a+b)t}
\end{aligned} \qquad \text{----------(10)}$$

or,

$$P_{12}(t) = \frac{a}{a+b}\left[1-e^{-(a+b)t}\right] \quad , \quad P_{11}(t) = 1 - P_{12}(t)$$

$$P_{21}(t) = \frac{b}{a+b}\left[1 - e^{-(a+b)t}\right] \quad , \quad P_{22}(t) = 1 - P_{21}(t)$$

Here, $P_{12}(t)$ and $P_{21}(t)$ provide the probabilities of transfers from 'negative' state to 'positive' state and vice-versa respectively, of individuals in terms of risk parameters a and b from one point to the other.

5.3 ESTIMATION OF PARAMETER.

The statistical problem is to estimate risk parameters, defined in the model. Let the population be consisted of initially N individuals. Consider each study unit of the population as an independent trial. On the basis of blood examination results, every individual at initial and subsequent follow-up is classified in one of the two states – S_1 and S_2. We further define N_1 and N_2 as the number of individuals detected to be 'negative' and 'positive' respectively, at initial survey out of N individuals examined. Similarly, N_{12} and N_{21} are defined as the number of 'positives' and 'negatives' respectively, detected at the second survey out of those found negative (N_1) and positive (N_2) respectively, at the first survey.

An individual in state S_i at time zero must be in any one of the S_j states at time t. Since, this process does not have any absorbing state, we have,

$$P_{i1}(t) + P_{i2}(t) = 1 \text{ ; for } i = 1, 2.$$

If P_1 and P_2 be the initial probabilities of an individual for being in state S_1 and S_2 states respectively and $P_{ij}(t)$ be the transition probabilities of transfer from state S_i to S_j during period t, the

likelihood of path of individuals of the population will be,

$$L = P_1^{N_1} \; P_2^{N_2} \left[P_{11}(t)\right]^{N_{11}} \left[P_{12}(t)\right]^{N_{12}} \left[P_{22}(t)\right]^{N_{22}}$$

$$\times \left[P_{21}(t)\right]^{N_{21}}$$

$$L = C.\left[P_{11}(t)\right]^{N_{11}}. \left[P_{12}(t)\right]^{N_{12}}. \left[P_{21}(t)\right]^{N_{21}}.$$

$$\times \left[P_{22}(t)\right]^{N_{22}} \qquad \text{----------(11)}$$

where C is the constant not depending upon parameters. Taking logarithm on both the sides of (11) and differentiating with respect to $P_{12}(t)$ and $P_{21}(t)$, the equations

$$\frac{\partial \log L}{\partial P_{12}(t)} = 0 \text{ and } \frac{\partial \log L}{\partial P_{21}(t)} = 0 \text{ give}$$

$$\left.\begin{aligned} \hat{P}_{12}(t) &= \frac{N_{12}}{N_1} = f_{12} \text{ (say)} \\ \hat{P}_{21}(t) &= \frac{N_{21}}{N_2} = f_{21} \text{ (say)} \end{aligned}\right\} \text{----------(12)}$$

Here, the two statistics f_{12} and f_{21} estimate unbiasedly $P_{12}(t)$ and $P_{21}(t)$ respectively. In the theory of estimation, these estimators are known as RBAN estimates

(Fix and Neyman, 1951). Finally, the risk parameters a and b can be estimated in terms of f_{12} and f_{21}.

Second and third equations of (10) from (12) can be written as,

$$\frac{a}{a+b}\left[1-e^{-(a+b)t}\right] = f_{12}$$

and

$$\frac{b}{a+b}\left[1-e^{-(a+b)t}\right] = f_{21} \qquad \text{----------(13)}$$

Solving equations (13) for a and b in terms of f_{12} and f_{21}, we have

$$\hat{a} = -\frac{f_{12}}{t(f_{12}+f_{21})}\log(1-f_{12}-f_{21})$$

$$\hat{b} = -\frac{f_{21}}{t(f_{12}+f_{21})}\log(1-f_{12}-f_{21}) \qquad \text{------(14)}$$

There are, in (14), two risks parameters - a and b. These are, in fact, infinitesimal transition probabilities. If time unit chosen is sufficiently small, these may be interpreted as transition rates per unit of time. Since, here, time unit has been considered to be a day (of 24 hours), a and b would, in fact, be daily malaria parasite incidence and recovery rates respectively.

Here it is of interest to note that estimation of a and b from (14) is possible only when $f_{12} + f_{21} < 1$. However, a situations may take place where $f_{12} + f_{21} \not< 1$. In such circumstances, it could be interpreted that either the parameters were not constant as assumed in the model or the process was not Markovian. However, empirically where the sample sizes are not very small, the case of $f_{12} + f_{21} \not< 1$ would seldom take place.

5.4 APPLICATION OF THE MODEL.

Illustration on application of the model developed here, requires relevant data from longitudinal studies. Since, the type of data required by the model here could not be made available in spite of our thorough search of published records on the subject, an investigation had to be undertaken, keeping our requirements of data in mind. It was carried-out in total population of two villages in district Jhansi (U.P.) with the available time and resources. The methods of survey and other relevant details are elaborated in Chapter VIII.

The observed frequencies of transitions - from malaria negative state to malaria positive state and vice-versa are given in Table 5.1.

TABLE 5.1

Observed transition frequencies and estimated daily malaria parasite incidence and recovery rates (based on Surveys* I-III) for the two sexes separately.

Sex	TRANSITION FREQUENCIES $f_{12}=\frac{N_{12}}{N_1}$	$f_{21}=\frac{N_{21}}{N_2}$	$(f_{12}+f_{21})$	$\log_e(1-f_{12}-f_{21})$	$-\frac{f_{12}}{t(f_{12}+f_{21})}$	$-\frac{f_{21}}{t(f_{12}+f_{21})}$	TRANSITION RATES Incidence $\hat{a}$	Recovery $\hat{b}$
Male	5/215	7/12	0.6066	-0.9329	-0.001278	-0.032061	0.001193	0.029908
Female	4/264	4/10	0.4152	-0.5364	-0.001216	-0.032117	0.000652	0.017228
Total	9/479	11/22	0.5188	-0.7315	-0.001208	-0.032125	0.000884	0.023498

* Difference between two consecutive surveys was observed, on an average, to be of 30 days; thus, giving t = 30.

Analysis shown in it considers only cases who could be studied for malaria in the two consecutive surveys. Estimated daily net malaria parasite incidence and recovery rates are also given in Table 5.1.

Results in respect of incidence rate indicate that in the area studied, about 9 individuals per 10,000 population – about 12 males per 10,000 males and about 7 females per 10,000 females, got fresh malaria infection including relapse, if any per day. As far as clearance of parasites from blood in the area was concerned, about 2% 'positives' – about 3% males and about 2% females – transferred to the 'negative' state daily. Incidence as well as recovery rates were relatively higher in males than females.

Table 5.2 gives observed malaria parasite rates based on 3 surveys (Surveys I-III) for males and females separately. About 4 persons were observed to be positive for malaria per 100 population. It may be seen that expected equilibrium parasite rate ($\hat{a} / (\hat{a} + \hat{b})$) is exactly the same as was actually observed. However, results in respect of actual and expected equilibrium parasite rates differed somewhat for the two sexes. The inverse of $\hat{b}$, here, may be interpreted as 'expected duration of a positive episode'.

TABLE 5.2

Observed malaria parasite rate and expected equilibrium parasite rate (based on Surveys I-III combined) for two sexes separately.

Sex	RISK OF TRANSITION $\hat{a}$	RISK OF TRANSITION $\hat{b}$	$(\hat{a} + \hat{b})$	$\frac{\hat{a}}{\hat{a} + \hat{b}}$	OBSERVED POSITIVES FOR PARASITES* Proportion	OBSERVED POSITIVES FOR PARASITES* rate (%)	EXPECTED EQUILIBRIUM** PARASITE RATE (%)
Male	0.001193	0.029908	0.031101	0.038343	31/684	4.53	3.83
Female	0.000652	0.017228	0.017880	0.036482	21/753	2.79	3.65
Total	0.000884	0.023498	0.024382	0.036241	52/1,437	3.62	3.62

* Based on positive cases, detected in surveys I-III.

** Percentage value of $\frac{\hat{a}}{\hat{a} + \hat{b}}$ provides expected equilibrium parasite rate.

TABLE 5.3

Observed and expected transition probabilities of malaria (based on Surveys I-III combined) for two sexes separately.

Sex	OBSERVED				ESTIMATED PROBABILITIES			
	f_{11}	f_{12}	f_{22}	f_{21}	$\hat{P}_{11}(t)$	$\hat{P}_{12}(t)$	$\hat{P}_{22}(t)$	$\hat{P}_{21}(t)$
Male	0.9767	0.0233	0.4167	0.5833	0.9767	0.0233	0.4166	0.5834
Female	0.9848	0.0152	0.6000	0.4000	0.9849	0.0152	0.5999	0.4000
Total	0.9812	0.0188	0.5000	0.5000	0.9815	0.0185	0.5000	0.4999

It was of about 34 days for males against 58 days in case of females. On an average, expected duration of positive episode in the population studied was observed to be 43 days.

Probabilities of transitions from malaria positive state to malaria negative state and vice-versa during one month period - observed and estimated - from the calculated values of risk parameters - are given in Table 5.3. It may be seen that the two estimated transition probabilities $\hat{P}_{12}(t)$ and $\hat{P}_{21}(t)$ are almost the same as actually observed.

5.5 DISCUSSION.

It has been well accepted that "most statements intended to convey precise information are capable of some mathematical developments" (Bailey, 1967). Further, the discussion that whether the epidemiology is an area of application of mathematical models has convincingly been answered in affirmative (Bailey, 1957; MacDonald, 1957; Srivastava, 1975).

The model developed here is based on certain basic assumptions which constitute simplification of the situation. The assumptions made herein consider

that, parallel to the force of malaria infection that acts at a point of time in the population, there is a reversible force too; and 'positives' become 'negative' or vice-versa at constant rates. Such assumptions are acceptable only when time unit considered is small. Assumption on constant rates of transition in a unit of time is relevant, as here, time unit has been considered to be a day.

The model should have been applied to a population, homogeneous in nature as regards exposure and immunity. In fact, in our case, model was applied to the population, defined on the basis of sex and area only, and no consideration of age could be made. This could have been because of very small number of positive cases observed. Indeed, increase in age also increases immunity, to some extent, against malaria in the individual (Pull and Grab, 1974) thus, indicating that infants and children might be more susceptible to malaria than adults and older people. Therefore, the population to which our model was applied can not be treated homogeneous strictly. The derived results might, thus, be only grossly precise.

Pull and Grab (1974) utilized simple and reversible catalytic models, developed by Muench (1959)

to study inoculation and prevalence rates of malaria in infants. The two methods based on stochastic processes and Life Table approach have been suggested and applied in Chapter IV for this purpose in infants' population. The present method enables one to study transition probabilities and daily malaria parasite incidence and recovery rates in general population. However, the incidence of malaria in infants, studied by present method may be higher than that estimated by any of the two methods suggested in Chapter IV; the reason being that the present method includes relapses, if any, in addition to fresh infections while our earlier method takes into account new infections only. Similarly, the estimated recovery rates includes true recovery and latency, if any. Further, both rates – incidence and recovery and transition probabilities are based on patent parasitaemia as assessed by standard method of blood examination.

Model provides satisfactory results in respect of monthly transition rates. The expected equilibrium parasite rates, estimated by the model were exactly similar to those actually observed. The 'expected duration of positive episode' was estimated to be of 43 days in the area. In malaria, caused by

P. vivax and P.falciparum, values of such parameters are of much significance. These may be useful indicators of intensities of transmission and of immune status of the population.

The results of present investigation are based on small sample, in which study-individuals were not selected randomly. This could have been because of limited time and resources available with us. Our results, therefore, have certain limitations and certainly can not be generalized for bigger populations. However, they may be taken to be true for the communities, resembling in nature with that studied by us. Further, an increase in sample size in the studies like present one undoubtedly auguments precision of the estimates, however, at the same time, it may decrease homogenecity of the sample.

The present model does not take into account the risk of 'lost to follow-up' cases and considers only individuals who could be studied in both the consecutive surveys. The estimated transition rates will, therefore, be 'net transition rates'.

Our model was applied to the parasitological data on malaria without considering different malaria species. Different species of malaria often have

considerably different epidemiological features and as such, the model should have been applied to the data pertaining to the specific malaria species separately. It was, however, done in view of only small number of positive cases of malaria observed in our field survey.

The model, developed and used here, is of great utility in understanding transmission mechanism of the disease and in selecting optimum control strategy to combat the malady in a population. It can also be used for describing actual malaria epidemiological situations and for predicting expected transition rates and probabilities of transitions in a homogeneous population when variations occur in the force of infection - either under natural conditions or under the influence of control programmes. It can also be applied to other epidemiological problems, such as - other parasitic diseases, that lend themselves to the description by the same model, using concept of reversible force and constant rates.

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CHAPTER VI

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA — CONSIDERATION OF 'LOST TO FOLLOW-UP' CASES.

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA — CONSIDERATION OF 'LOST TO FOLLOW-UP' CASES.

In Chapter V, a stochastic model has been suggested for the estimation of transition rates of malaria from follow-up studies, carried-out in general population. The method outlined provided a simple and practicable tool for studying malaria situations in the area. The suggested model, however, is based on the assumption that all individuals who had been initially examined for malaria are covered, in toto, at subsequent follow-ups which is seldom the case.

In developing countries like India where literacy rate is still very low, the task of conducting field studies involving blood collection for examination of total population is notoriously difficult indeed. In rural communities of India, despite the sincere efforts by investigators and high motivations, the satisfactory coverage in the field-surveys is usually not achieved and that, in subsequent follow-ups,

a significant proportion of the population, studied initially is often 'lost to follow-up' in view of many reasons - 'could not be traced because of being dead', 'moved to some other place permanently', 'not available at the time of visit' and 'available but refused to cooperate' etc. Such individuals form a category of 'lost to follow-up cases'.

Individuals who were detected to be free from malaria initially are at the risk to suffer from it during their follow-up periods. Similarly, those found positive for malaria in the first survey, may not show any evidence of positive parasitaemia in blood at their subsequent follow-ups. Furthermore, because of reasons indicated in the previous paragraph, each individual of the population, irrespective of his state at initial survey, besides being at these two risks at the time of subsequent follow-ups, is also at the risk of 'lost to follow-up'. Consideration of such a risk may be made while estimating epidemiological rates of malaria from longitudinal studies. Here, earlier model which is based on only two states has been extended to consider 'lost to follow-up' case as the competing risk.

6.1 FIRST METHOD OF APPROACH.

6.1.1 ASSUMPTIONS.

Let the longitudinal study be conducted in a homogeneous population during defined period of time; we consider following assumptions.

(i) Individuals of the population under study are exposed to the risk of malaria during the period of observation.

(ii) During the time of follow-up of the studied population, risk of 'lost to follow-up' is present. Thus, it is assumed that a few cases who were studied initially are 'lost' during the follow-up time.

(iii) Individuals' transitions from one state to the other are independent of their past transitions, if any.

(iv) The probability of making one transition — from negative to positive state or to the 'lost to follow-up' state, or from positive state to any of the rest two defined states — in a single unit of time is very small and that, probability of making more than one transition

in a single unit of time is negligible. This assumption clearly indicates that, in an unit of time, only one transition from one state to the other can take place.

(v) Malaria infection and vector are constantly present in the environment.

6.1.2 THE MODEL.

Let t be the length of interval between time points of two consecutive surveys such that the changes, if any, in the probabilities of risk during this period may be neglected. Further, this interval may further be divided into, many elementary time-intervals of length τ. These elementary time-intervals are considered to be so short that an individual exposed to various risks meets with only one risk during the interval τ. This assumption in longitudinal studies on malaria is quite relevant as one single day (24 hours) may easily be taken as τ.

We postulate following 3 states.

S_1 : State of being free from malaria.

S_2 : State of being positive for malaria.

S_3 : State of being 'lost to follow-up' or dead from the causes not connected with malaria.

FLOW CHART OF A MALARIA MODEL BASED ON THREE STATES - SHOWING POSTULATED NUMBER OF STATES AND POSSIBILITIES OF TRANSITIONS.

S.NO.	STATE	CONSIDERED TIME INTERVAL 0.....τ.....t
1.	FREE FROM MALARIA	
2.	POSITIVE FOR MALARIA	
3.	'LOST TO FOLLOW-UP' OR DEAD FROM CAUSES OTHER THAN MALARIA.	

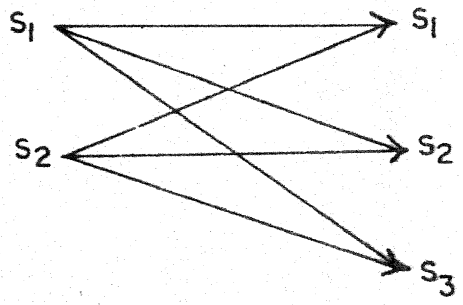


FIGURE 6·1

The possibilities of transitions from one state to the other may be shown graphically as indicated in Figure 6.1. The system of states is easily understandable. At subsequent follow-ups, an individual who was initially 'positive' or 'negative' may remain in the original state or leave original state and join malaria negative and positive states respectively; he may be 'lost to follow-up' or dead from the causes not connected with malaria. The transition probabilities during the period of observation will depend upon t and intensities of risk. Such intensities are considered to be constant as given below.

State S_i	State S_j		
	S_1	S_2	S_3
S_1	$-(a_1+a_2)$	a_1	a_2
S_2	b_1	$-(b_1+b_2)$	b_2

--------(1)

Here, constants a and b are related with frequency of transfers between states. Thus, a greater value of these constant intensities will mean frequent transfers from states S_i to S_j and their zero value will indicate that transfers are not possible.

The intensities, in general, and particularly in cases where the considered time unit is large are functions of time. However, here, they have been considered to be independent of time. This assumption, is quite relevant as t is measured in terms of days which is so small that changes in them, if any, may be neglected. Further, for the purpose of simplicity, the time point of initial survey is considered to be zero and of subsequent follow-up as t; the length of period (0, t) may, thus, be denoted by t.

Following steps, envisaged in the Chapter V, the Kolmogorow differential equations of probabilities of transfers from S_i to S_j may be given as,

$$\left.\begin{aligned}
\frac{\partial}{\partial t}P_{11}(t) &= -(a_1+a_2)\,P_{11}(t) + b_1P_{12}(t) \\
\frac{\partial}{\partial t}P_{12}(t) &= a_1P_{11}(t) - (b_1+b_2)\,P_{12}(t) \\
\frac{\partial}{\partial t}P_{22}(t) &= -(b_1+b_2)\,P_{22}(t) + a_1P_{21}(t) \\
\frac{\partial}{\partial t}P_{21}(t) &= b_1P_{22}(t) - (a_1+a_2)\,P_{21}(t)
\end{aligned}\right\} \quad \text{------(2)}$$

The initial conditions for equations(2) are,

$$\left.\begin{aligned}
&P_{11}(0) = P_{22}(0) = 1 \\
\text{and} \qquad & \\
&P_{12}(0) = P_{21}(0) = 0
\end{aligned}\right\} \quad \text{----------(3)}$$

Equations (2) are linear first order differential equations with constant coefficients; they may have a solution of the form.

$$P_{ij}(t) = C_{ij}e^{rt} \qquad \text{----------(4)}$$

Substituting (4) in (2) and solving, we obtain

$$\left.\begin{aligned} C_{11}(r + a_1 + a_2) - b_1C_{12} &= 0 \\ C_{12}(r + b_1 + b_2) - a_1C_{11} &= 0 \\ C_{22}(r + b_1 + b_2) - a_1C_{21} &= 0 \\ C_{21}(r + a_1 + a_2) - b_1C_{22} &= 0 \end{aligned}\right\} \qquad \text{---------(5)}$$

and

Equations (5) will have an unique solution, only when,

$$\begin{vmatrix} (r + a_1 + a_2) & -b_1 \\ -a_1 & (r + b_1 + b_2) \end{vmatrix} = 0$$

Solution of determinant gives two values of r, denoted here, by r_1 and r_2.

$$r_1 = -\tfrac{1}{2}(a_1+a_2+b_1+b_2) + \tfrac{1}{2}\sqrt{(a_1+a_2-b_1-b_2)^2 + 4a_1b_1}$$

$$r_2 = -\tfrac{1}{2}(a_1+a_2+b_1+b_2) - \tfrac{1}{2}\sqrt{(a_1+a_2-b_1-b_2)^2 + 4a_1b_1}$$

Since in (5), coefficients C_{ij} are related for each value of r_k (for k = 1, 2), they, after rearranging, can be written as

$$C_{11k} = A_k\,(r_k + b_1 + b_2),\quad C_{22k} = B_k\,(r_k + a_1 + a_2)$$
$$C_{12k} = A_k\,a_1 \qquad ,\quad C_{21k} = B_k\,b_1 \qquad \text{---(6)}$$

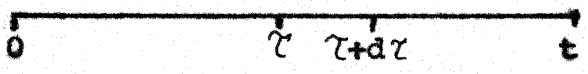
Where A_k and B_k are two arbitrary constants. Utilizing values of C_{ij} from (6) in (4) and using initial conditions of (3), we get following values of A_k and B_k.

$$A_1 = B_1 = \frac{1}{(r_1-r_2)}$$
$$A_2 = B_2 = \frac{1}{(r_1-r_2)} \qquad \text{----------(7)}$$

The transition probabilities are, thus, obtained as,

$$P_{11}(t) = \frac{1}{(r_1-r_2)}\left[(r_1+b_1+b_2)\,e^{r_1t} - (r_2+b_1+b_2)\,e^{r_2t}\right]$$
$$P_{12}(t) = \frac{a_1}{(r_1-r_2)}\left[e^{r_1t} - e^{r_2t}\right]$$
$$P_{22}(t) = \frac{1}{(r_1-r_2)}\left[(r_1+a_1+a_2)\,e^{r_1t} - (r_2+a_1+a_2)\,e^{r_2t}\right] \qquad (8)$$
$$P_{21}(t) = \frac{b_1}{(r_1-r_2)}\left[e^{r_1t} - e^{r_2t}\right]$$

Similarly, probabilities of transitions from state S_i (for i = 1,2) to S_3 where S_3 is a terminal state, can also be easily worked-out. An individual who is in state S_i initially may reach the state of 'lost to follow-up' either directly from S_1 or by way of S_2. Similarly, an individual in state S_2 at time zero may pass to S_3 in two mutually exclusive ways — either $S_2 \rightarrow S_3$ or $S_2 \rightarrow S_1 \rightarrow S_3$. Further, the individual who is in S_3 at time t might have reached S_3 at any time prior to t. We consider infinitesimal time interval $(\tau, \tau+d\tau)$ for fixed τ, $0 < \tau \leq t$.



The probabilities of transitions that an individual, who at time zero is in state S_1 and S_2 respectively will reach S_3 within time interval $(\tau, \tau+d\tau)$ will, thus, be

$$\left.\begin{array}{l} a_2 P_{11}(\tau)d\tau + b_2 P_{12}(\tau)d\tau \\ \text{and} \\ b_2 P_{22}(\tau)d\tau + a_2 P_{21}(\tau)d\tau \end{array}\right\} \quad \text{----------(9)}$$

The transition probabilities $P_{13}(t)$ and $P_{23}(t)$ may be written as,

$$P_{13}(t) = a_2 \int_0^t P_{11}(\tau)d\tau + b_2 \int_0^t P_{12}(\tau)d\tau$$

$$P_{23}(t) = b_2 \int_0^t P_{22}(\tau)d\tau + a_2 \int_0^t P_{21}(\tau)d\tau \qquad \text{------(10)}$$

Substituting values of $P_{ij}(\tau)$ from (8) in (10) and integrating, we finally obtain,

$$P_{13}(t) = \frac{1}{(r_1-r_2)} \left[(a_1+b_1+b_2)\ (e^{r_2 t} - e^{r_1 t}) - (r_1 e^{r_1 t} + r_2 e^{r_2 t}) + (r_1-r_2)\right]$$

$$P_{23}(t) = \frac{1}{(r_1-r_2)} \left[(a_1+a_2+b_1)\ (e^{r_2 t} - e^{r_1 t}) - (r_1 e^{r_1 t} + r_2 e^{r_2 t}) + (r_1-r_2)\right] \qquad \text{------(11)}$$

It may be seen that the transition probabilities,

$$P_{11}(t) + P_{12}(t) + P_{13}(t) = 1$$

and

$$P_{21}(t) + P_{22}(t) + P_{23}(t) = 1$$

Here, equations derived in (8) provide a method for estimating transition rates of malaria in the presence of risk of 'lost to follow-up'. These probabilities $P_{ij}(t)$ would provide, in fact,

'crude rates' or 'gross rates' of risk. Here the adjective 'crude' or 'gross' emphasizes that the contemplated transfers from S_i to S_j is affected by other risks competing with this particular risk. Thus, for example, under the assumption that an individual originally in free-from-malaria state, during time t, is subject to risk of transfer to malaria-positive state and thence, to 'lost to follow-up' state. In the similar fashion, another individual who is positive for malaria in the beginning, during the time-period t is subject to the risk of becoming 'negative' and then being 'lost to follow-up'. Naturally, the presence of risks $S_1 \rightarrow S_2 \rightarrow S_3$ and $S_2 \rightarrow S_1 \rightarrow S_3$ deminishes the risk of transfer of individuals from $S_1 \rightarrow S_2$ and $S_2 \rightarrow S_1$ respectively. Furthermore, the decrease in the risks $S_1 \rightarrow S_2$ and $S_2 \rightarrow S_1$ is artificial as it depends upon freuqencies of losses and has nothing to do with the risk of suffering from or getting rid of malaria. The case of the estimation of net malaria transition rates has already been discussed in Chapter V; such rates however, can directly be derived from present gross rates, as given below.

The Net Malaria Transition Rates.

The net probability is defined (Chiang, 1968) as the probability of happening of an event if the specific risk is the only risk in effect in the population. Conversely, it is the probability of occurrence of an event if the specific risk is eliminated from the population. Thus, here, probability of transfers from $S_1 \longrightarrow S_2$ and $S_2 \longrightarrow S_1$ under the assumption that risks $S_1 \longrightarrow S_3 = S_2 \longrightarrow S_3 = 0$, would provide net malaria transition rates respectively, with risks of transfer $S_1 \longrightarrow S_3$ and $S_2 \longrightarrow S_3$ being eliminated. For simplicity, we denote such rates, during time t, by $P_{ij.}(t)_{13,23,}$ for i, j, = 1,2. These are readily obtained by putting $a_2 = b_2 = 0$ in equations (8). Net malaria transition rates are, thus, obtained as ;

$$P_{12.}(t)_{13,23} = \frac{a_1}{a_1+b_1}\left[1 - e^{-(a_1+b_1)t}\right]$$

$$P_{21.}(t)_{13,23} = \frac{b_1}{a_1+b_1}\left[1 - e^{-(a_1+b_1)t}\right] \qquad \text{-------(12)}$$

It may be seen that probability $P_{12.}(t)_{13,23}$ and $P_{21.}(t)_{13,23}$ are the same as the probabilities $P_{12}(t)$ and $P_{21}(t)$ of Chapter V, if intensities of risks a_1 and b_1 are replaced by a and b respectively.

Such rates are of utmost significance in the evaluation of the effectiveness of different types of malaria control and eradication programmes.

6.1.3 ESTIMATION OF PARAMETER.

In a population of size N, if Ni be the number entering the state S_i, for i = 1,2 and N_{ij} be the total transitions from S_i to S_j, for i = 1,2 and j = 1,2,3, then the likelihood of the observed path, will be,

$$L = C \left[P_{11}(t)\right]^{N_{11}} \left[P_{12}(t)\right]^{N_{12}} \left[P_{13}(t)\right]^{N_{13}}$$

$$\times \left[P_{21}(t)\right]^{N_{21}} \left[P_{22}(t)\right]^{N_{22}} \left[P_{23}(t)\right]^{N_{23}} \quad \text{----(13)}$$

Taking logarithm on both the sides of equation (13) and differentiating partially with respect to $P_{12}(t)$ and $P_{21}(t)$ respectively, we get following equations.

$$\frac{\partial \log L}{\partial P_{12}(t)} = \frac{\partial \log L}{\partial P_{21}(t)} = 0 \quad \text{----------(14)}$$

Writing, $N_1-N_{12}-N_{13}$ and $N_2-N_{21}-N_{23}$ for N_{11} and N_{22} respectively, and

$1 - P_{12}(t) - P_{13}(t)$ and $1 - P_{21}(t) - P_{23}(t)$ for $P_{11}(t)$ and $P_{22}(t)$ respectively, we, after rearranging, can write equations (14) as,

$$\left.\begin{aligned}(N_1 - N_{13})\, P_{12}(t) + N_{12}\, P_{13}(t) &= N_{12} \\ (N_1 - N_{12})\, P_{13}(t) + N_{13}\, P_{12}(t) &= N_{13}\end{aligned}\right\} \quad \text{---------(15)}$$

Solutions of equations (15) leads to the maximum likelihood estimates of $P_{ij}(t)$ as given below :

$$\hat{P}_{ij}(t) = \frac{N_{ij}}{N_{i1} + N_{i2} + N_{i3}}$$

or

$$\hat{P}_{ij}(t) = \frac{N_{ij}}{N_i} \quad , \text{ for } \begin{matrix} i = 1,2 \\ j = 1,2,3. \end{matrix}$$

Estimation of risk parameters in terms of observed values is essential to work-out daily malaria transition rates. Like Chapter V, an attempt here also was made to carry-out maximum likelihood estimates of risk parameters - a and b. However, they did not seem feasible in view of voluminous calculations involved. An alternative method was, therefore, considered.

6.2 ALTERNATIVE METHOD OF APPROACH.

The method of approach, detailed above is based on customary scheme for follow-up studies. It is simple to understand and provides formulae for gross transition probabilities in terms of intensities of

risks from one state to the other. The calculations involved in the estimation of risk parameters, however, seem to be voluminous; the method, thus, does not provide practicable formulae for estimating daily malaria gross incidence and recovery rates.

This method of approach considers possibilities of multiple transitions from one state to the other within any given interval. The method is based on the assumption that only one transition during the period (0, t) from one state to the other is possible. It is assumed that our follow-up procedure will be able to establish, out of N_1 initially 'negatives', a number $N_1 f_{11}$ who remained negative without having suffered from a relapse or a fresh malaria attack. A second category with number $N_1 f_{12}$ of persons who suffered a single relapse or fresh malaria morbidity and at the conclusion of the period of observation were in S_2. We also expect it to be possible to determine the third frequency $N_1 f_{13}$ who were 'lost to follow-up' in view of several reasons at time t.

Similarly, with regard to N_2 who were initially 'positive', we hope to establish successfully different categories of persons. Thus, in the similar

fashion, first category will be consisting of N_2f_{22} persons who at time t were still in S_2 without having had any malaria free life. N_2f_{21} will denote those who had single transition from S_2 to S_1 and at the time of conclusion, were in S_1. Finally, N_2f_{23} includes those initially 'positive' cases who had been 'lost to follow-up' at time t.

As stated earlier, N_i is the number entering the state S_i and N_{ij} being the number of transitions from state S_i to S_j. Since only one transition from one state to the other is possible during (0, t), frequencies N_{11}, N_{12} and N_{13} can easily be interpreted as N_1f_{11}, N_1f_{12} and N_1f_{13} respectively. Similarly, frequencies N_{22}, N_{21} and N_{23} would be equal to N_2f_{22}, N_2f_{21} and N_2f_{23} respectively.

Suppose i stands for either 0 or 1, and $j = 1,2,3$. If l is any non negative integer, then the symbol $P_{ij.l}(t)$ would represent the probability that an individual while in S_i will be transferred to S_j exactly l times between interval (0, t) and at time t, he will be found in S_j. Further, since our assumption of only one transition between (0, t), ensures that more than one transitions are not at all possible, l will take only two values 0 or 1. Thus, only two types of probabilities — $P_{ij.0}^{(t)}$ and

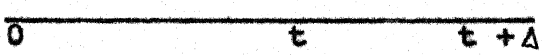
$P_{ij.1}^{(t)}$ are possible in interval (0, t) with the following initial conditions.

$$P_{ij.0}^{(0)} = 1,\ P_{ij.1}^{(0)} = 0,\ \text{for } i = j$$

and

$$P_{ij.0}^{(0)} = 0,\ P_{ij.1}^{(0)} = 0,\ \text{for } i \neq j$$

Following steps envisaged in Chapter V, the probabilities of transitions at any point of time τ, for $0 \leq \tau \leq t$ from S_1 to S_2 and S_2 to S_1 can be defined in terms of risk parameters a and b respectively.



Now, considering contiguous time interval (0, t) and (t, t +Δ), the probabilities $P_{ij.0}^{(t+\Delta)}$ and $P_{ij.1}^{(t+\Delta)}$, for i,j = 1,2 can be expressed as follows.

$$P_{11.0}^{(t+\Delta)} = P_{11.0}^{(t)}\ P_{11.0}^{(\Delta)}$$

$$= P_{11.0}^{(t)} \left[1 - \Delta a_1 - \Delta a_2 - 0(\Delta)\right] \text{--------(1)}$$

Subtracting $P_{11.0}^{(t)}$ from both the sides of the equation (1) and taking limit as $\Delta \rightarrow 0$, we have

$$\frac{\partial}{\partial t} P_{11.0}^{(t)} = -(a_1+a_2) P_{11.0}^{(t)}$$

Similarly,

$$\frac{\partial}{\partial t} P_{22.0}^{(t)} = -(b_1+b_2) P_{22.0}^{(t)} \qquad \text{------(2)}$$

In the similar fashion,

$$P_{12.1}^{(t+\Delta)} = P_{11.0}^{(t)} P_{12.1}^{(\Delta)} + P_{12.1}^{(t)} P_{22.0}^{(\Delta)}$$

$$= P_{11.0}^{(t)} \left[a_1\Delta + 0(\Delta)\right] + P_{12.1}^{(t)} \qquad (3)$$

$$\times \left[1-b_1\Delta-b_2\Delta-0(\Delta)\right]$$

Subtracting $P_{12.1}^{(t)}$ from both the sides of equation (3) and taking limit as $\Delta \longrightarrow 0$, we have

$$\frac{\partial}{\partial t} P_{12.1}^{(t)} = a_1 P_{11.0}^{(t)} - (b_1+b_2) P_{12.1}^{(t)}$$

and similarly,

$$\frac{\partial}{\partial t} P_{21.1}^{(t)} = b_1 P_{22.0}^{(t)} - (a_1+a_2) P_{21.1}^{(t)} \qquad \text{-------(4)}$$

Solution of equation (2) is quite simple; by integrating and applying initial conditions, we get

$$P_{11.0}^{(t)} = e^{-(a_1+a_2)t}$$

and

$$P_{22.0}^{(t)} = e^{-(b_1+b_2)t} \qquad \text{----------(5)}$$

In order to solve equations (4), we rewrite first equation

$$\frac{\partial}{\partial t} P_{21.1}^{(t)} + (b_1+b_2)\, P_{12.1}^{(t)} = a_1\, P_{11.0}^{(t)}$$

It is first order linear, differential equation. Multiplying it by $e^{(b_1+b_2)t}$, we have

$$\frac{\partial}{\partial t} P_{12.1}^{(t)}\, e^{(b_1+b_2)t} = \left[a_1\, P_{11.0}^{(t)} e^{(b_1+b_2)t} - (b_1+b_2) e^{(b_1+b_2)t}\, P_{12.1}^{(t)}\right]$$

or

$$\frac{\partial}{\partial t}\left[P_{12.1}^{(t)} e^{(b_1+b_2)}\right] = a_1\, e^{(b_1+b_2-a_1-a_2)t}$$

Integrating on both the sides, we have

$$P_{12.1}(t)\, e^{(b_1+b_2)t} = a_1\, e^{(b_1+b_2-a_1-a_2)t} + C \quad \text{-------(6)}$$

Applying initial conditions and solving, we get

$$C = -\frac{a_1}{(b_1+b_2-a_1-a_2)}$$

Putting value of C in (6), we finally have

$$P_{12.1}(t) = \frac{a_1}{(b_1+b_2-a_1-a_2)}\left[e^{-(a_1+a_2)t} - e^{-(b_1+b_2)t}\right] \text{---(7)}$$

Similarly, we obtain,

$$P_{21.1}(t) = \frac{b_1}{(b_1+b_2-a_1-a_2)} \left[e^{-(a_1+a_2)t} - e^{-(b_1+b_2)t} \right] \text{---(8)}$$

The probabilities of transitions to 'lost to follow up' state can also be worked-out following the similar convention. Considering contiguous time interval, (0, t) and (t, t + Δ)

$$P_{13.1}(t+\Delta) = \left[P_{13.1}(t)\, P_{33.0}(\Delta) + P_{11.0}(t)\, P_{13.1}(\Delta) + P_{12.1}(t)\, P_{23.1}(\Delta) \right]$$

Since S_3 is a terminal state $P_{33.0}(\Delta) = 1$. Subtracting $P_{13.1}(t)$ from both the sides and taking limit as $\Delta \rightarrow 0$, we have,

$$\frac{\partial}{\partial t} P_{13.1}(t) = a_2\, P_{11.0}(t) + b_2\, P_{12.1}(t) \quad \text{----------(9)}$$

Putting values of $P_{11.0}(t)$ and $P_{12.1}(t)$ from (5) and (7) in (9) and integrating, we obtain

$$P_{13.1}(t) = \frac{a_2}{(a_1+a_2)} \left[1 - e^{-(a_1+a_2)t} \right] + \frac{a_1\, b_1}{(a_1+a_2)\,(b_1+b_2)} \times \left[1 - \frac{(b_1+b_2)\, e^{-(a_1+a_2)t} - (a_1+a_2)\, e^{-(b_1+b_2)t}}{(b_1+b_2-a_1-a_2)} \right] \text{---(10)}$$

Similarly,

$$\frac{\partial}{\partial t} P_{23.1}(t) = b_2\, P_{22.0}(t) + a_2\, P_{21.1}(t) \quad \text{----------(11)}$$

By putting values of $P_{22.0}(t)$ and $P_{21.1}(t)$ from (5) and (8) in (11), we finally obtain

$$P_{23.1}(t) = \frac{b_2}{(b_1+b_2)}\left[1 - e^{-(b_1+b_2)t}\right] + \frac{b_1\, a_2}{(a_1+a_2)\,(b_1+b_2)}$$

$$\times \left[1 - \frac{(b_1+b_2)\; e^{-(a_1+a_2)t} - (a_1+a_2)\; e^{-(b_1+b_2)t}}{(b_1+b_2 - a_1-a_2)}\right] \text{----(12)}$$

6.2.1 ESTIMATION OF PARAMETERS.

Like earlier, we assume that in the beginning of interval (0, t), N_i individuals are in S_i, for $i = 1,2$. These two groups form a system of independent trials. At time t, let N_i individuals be categorized as below.

For N_i individuals in S_i at the beginning, we define,

N_{11} : Individuals, who were negative for malaria initially, remained negative at time t <u>without having suffered from a relapse or fresh malaria attack</u>.

N_{12} : Individuals who were initially negative for malaria, <u>suffered from one malaria relapse or fresh attack and were found in S_2 at time t.</u>

N_{13} : Number of initially 'negatives' who were 'lost to follow-up' at time t.

Similarly, for N_2 in S_2, we define,

N_{22} : Individuals who were positive for malaria in the beginning, remained positive <u>without having had any malaria free state</u>.

N_{21} : Initially 'positives' who had <u>single transition from S_2 to S_1 and at time t, they were found in S_1</u>.

N_{23} : Initially 'positives' who were 'lost to follow-up' at time t.

Now, because more than one transitions are not possible, and f_{ij} is defined as,

$$f_{ij} = \frac{N_{ij}}{N_i} \text{ , for } i = 1,2 \quad j = 1,2,3.$$

The maximum likelihood estimate of $P_{ij.1}(t)$ can easily be worked-out like (6.1.3). It would be

$$\hat{P}_{ij.1}(t) = f_{ij} \text{ , for } 1 = 0,1. \quad \text{----------(13)}$$

Putting values of $P_{ij.1}(t)$ in (5), (7) and (8), we obtain

$$e^{-(a_1+a_2)t} = f_{11}$$
$$e^{-(b_1+b_2)t} = f_{22} \qquad \text{----------(14)}$$

and

$$\frac{a_1}{(b_1+b_2 - a_1-a_2)}\left[e^{-(a_1+a_2)t} - e^{-(b_1+b_2)t}\right] = f_{12}$$
$$\frac{b_1}{(b_1+b_2 - a_1-a_2)}\left[e^{-(a_1+a_2)t} - e^{-(b_1+b_2)t}\right] = f_{21} \qquad \text{---(15)}$$

Solving equations (14), we get

$$(a_1+a_2) = \frac{-\log f_{11}}{t}$$
$$(b_1+b_2) = \frac{-\log f_{22}}{t} \qquad \text{----------(16)}$$

Solution of equations (15) and (16) gives the estimates of intensities of risks. Thus,

$$\hat{a}_1 = \frac{f_{12}}{t(f_{11}-f_{22})}(\log f_{11} - \log f_{22})$$

$$\hat{b}_1 = \frac{f_{21}}{t(f_{11}-f_{22})}(\log f_{11} - \log f_{22})$$

$$\hat{a}_2 = \frac{-\log f_{11}}{t} - \frac{f_{12}}{t(f_{11}-f_{22})}(\log f_{11} - \log f_{22}) \qquad (17)$$

$$\hat{b}_2 = \frac{-\log f_{22}}{t} - \frac{f_{21}}{t(f_{11}-f_{22})}(\log f_{11} - \log f_{22})$$

Here, $\hat{a}_1$ and $\hat{b}_1$ provide gross estimates of daily malaria incidence and recovery rates respectively.

6.2.2 APPLICATION OF THE MODEL.

Application of the model, formulated in Section 6.2 has been illustrated in Tables 6.1 to 6.5. The model has been applied to the data collected in a longitudinal study on malaria morbidity, carried-out in a rural population of Jhansi district (U.P.), specifically undertaken to obtain relevant data to judge the suitability of the model. It seemed essential to undertake such a study for the purpose when review of a good amount of literature on the subject failed to provide desired type of data. The methods of survey, population covered and other important details have been given in Chapter VIII.

The observed transition frequencies from one state to the other, based on data obtained from surveys I-III, are given in Table 6.1. Such frequencies clearly indicate that significant proportion of 'positive' and 'negative' cases could not be studied as many cases were 'lost to follow-up' because of many reasons. The consideration of such 'lost to follow-up' cases may, at times, be important while interpreting malaria parasite incidence and recovery rates in different population groups.

TABLE 6.1

Observed frequencies of transitions from one state to the other (based on Surveys - I-III) for the two sexes separately.

Sex	TRANSITIONS FROM STATE S_1 TO S_j, j = 1,2,3.				TRANSITIONS FROM STATE S_2 TO S_j, j=1,2,3			
	No. of 'negatives' studied	$f_{11} = \frac{N_{11}}{N_1}$	$f_{12} = \frac{N_{12}}{N_1}$	$f_{13} = \frac{N_{13}}{N_1}$	No. of 'positives' studied	$f_{22} = \frac{N_{22}}{N_2}$	$f_{21} = \frac{N_{21}}{N_2}$	$f_{23} = \frac{N_{23}}{N_2}$
Male	580	210/580	5/580	365/580	29	5/29	7/29	17/29
Female	648	260/648	4/648	384/648	18	6/18	4/18	8/18
Total	1,228	470/1,228	9/1,228	749/1,228	47	11/47	11/47	25/47

TABLE 6.2

Logarithm of observed monthly transition probabilities (f_{ij}) from one state to the other for the two sexes separately.

Sex	TRANSITIONS FROM S_1 TO S_j, j = 1,2,3			TRANSITIONS FROM S_2 TO S_j, j = 1,2,3		
	$\log_e f_{11}$	$\log_e f_{12}$	$\log_e f_{13}$	$\log_e f_{22}$	$\log_e f_{21}$	$\log_e f_{23}$
Male	-1.0158	-4.7560	-0.4632	-1.7579	-1.4213	-0.5341
Female	-0.9133	-5.0832	-0.5232	-1.0987	-1.5042	-0.8108
Total	-0.9605	-4.9199	-0.4945	-1.4524	-1.4524	-0.6313

The estimated values of risk parameters a and b have been shown in Table 6.2. Here, these values like earlier, are indeed, infinitesimal transition probabilities from one state to the other. Since, period of one day can easily be treated to be sufficiently small in malaria studies, $\hat{a}_1$ and $\hat{b}_1$ can thus, be regarded as daily malaria parasite incidence and recovery rates respectively. The values of $\hat{a}_2$ and $\hat{b}_2$ would, however, indicate the daily rates of 'lost to follow-up' from malaria negative and positive states respectively. Since the presence of $\hat{a}_2$ and $\hat{b}_2$ has been taken into consideration in calculation of $\hat{a}_1$ and $\hat{b}_1$, the latter would, in fact, give 'gross' or 'crude' malaria transition rates.

Analysis of Table 6.3 indicates an overall daily gross incidence rate of about 8 per 10,000 population – about 11 per 10,000 for males against 6 per 10,000 for females. Gross recovery rates were considerably higher than corresponding incidence rates for two sexes separately. Overall daily gross recovery rate was 26 per 1000 in the community studied; these were about 31 per 1,000 and 20 per 1,000 for males and females respectively.

With the view to assess the suitability of the model discussed in Section 6.2, probabilities of transitions from malaria negative state to malaria positive state and vice-versa for a period of 30 days were worked-out. Such probabilities, estimated in terms of risk parameters, and those actually observed have been shown in Table 6.4. It may be seen from this table that observed and estimated monthly probabilities of transitions are almost the same, indicating that model shows a good fit to the observed data.

Expected equilibrium parasite rates utilizing values of daily gross incidence and recovery rates have also been calculated. Such rates - observed and expected - for two sexes separately have been shown in Table 6.5. Analysis indicates a gross expected equilibrium parasite rate of about 3%; it was almost similar in the two sexes. Furthermore, the 'expected duration of positive episode' was estimated considering the inverse of gross recovery rates for males and females separately. Overall 'expected duration of positive episode' was observed to be of 39 days; it was of 32 days for males against 49 days for females.

TABLE 6.3

Estimated values* of risk parameters 'a' and 'b' for the two sexes separately.

Sex	f_{12}	f_{21}	$t(f_{11}-f_{22})$	$(\log_e f_{11}-\log_e f_{22})$	VALUES OF RISK PARAMETERS			
					$\hat{a}_1$	$\hat{b}_1$	$\hat{a}_2$	$\hat{b}_2$
Male	0.0086	0.2414	5.6910	0.7421	0.001121	0.031478	0.032739	0.027119
Female	0.0062	0.2222	2.0370	0.1854	0.000564	0.020234	0.029879	0.016389
Total	0.0073	0.2340	4.4610	0.4919	0.000805	0.025802	0.031212	0.022611

* Like Chapter V, value of 't' here also has been taken to be 30 days.

TABLE 6.4

Observed and estimated monthly gross malaria transition probabilities from one state to the other for the two sexes separately.

Sex	Observed Probabilities			Estimated Probabilities		
	Transitions from state S_i to state S_j, $j = 1,2,3$					
	f_{11}	f_{12}	f_{13}	$\hat{P}_{11.0}(t)$	$\hat{P}_{12.1}(t)$	$\hat{P}_{13.1}(t)$
Male	0.3621	0.0086	0.6293	0.3621	0.0086	0.6225
Female	0.4012	0.0062	0.5925	0.4012	0.0062	0.5899
Total	0.3827	0.0073	0.6099	0.3826	0.0073	0.6057
	Transitions from state S_2 to state S_j, $j = 1,2,3$.					
	f_{22}	f_{21}	f_{23}	$\hat{P}_{22.0}(t)$	$\hat{P}_{21.1}(t)$	$\hat{P}_{23.1}(t)$
Male	0.1724	0.2414	0.5862	0.1724	0.2414	0.5794
Female	0.3333	0.2222	0.4444	0.3333	0.2223	0.4416
Total	0.2340	0.2340	0.5319	0.2340	0.2340	0.5276

TABLE 6.5

Observed malaria parasite rate and expected equilibrium parasite rate (based on Surveys I-III) for the two sexes separately.

Sex	$\hat{a}_1$	$\hat{b}_1$	$(\hat{a}_1+\hat{b}_1)$	$\frac{\hat{a}_1}{\hat{a}_1+\hat{b}_1}$	Observed parasite rate* (%)	Expected equilibrium# parasite rate (%)	$\frac{1}{\hat{b}_1}$ ●
Male	0.001121	0.031478	0.032599	0.034388	4.53	3.43	31.8
Female	0.000564	0.020234	0.020798	0.027118	2.79	2.71	49.4
Total	0.000805	0.25802	0.026607	0.030252	3.62	3.02	38.8

* Based on positive cases, detected in surveys I - III.

\# Percentage value of $\frac{\hat{a}_1}{\hat{a}_1+\hat{b}_1}$ provides expected equilibrium parasite rate.

● $\frac{1}{\hat{b}_1}$ indicates 'expected duration of positive episode'.

DISCUSSION.

In epidemiological studies on malaria, the net malaria parasite incidence and recovery rates are undoubtedly important, however, their calculation does not consider presence of risk of 'lost to follow-up' of cases which is usually the case in follow-up studies on the subject. The gross malaria rates are calculated taking presence of risk of 'lost to follow-up' of cases into account. Such rates are of great significance in malaria studies as the risk of 'lost to follow-up' of cases in such studies remains usually considerably high.

The model, formulated in Section 6.1 provides simple formulae for estimation of transition probabilities for a specified period in terms of risk parameters. This model, indeed, is a simple extension of the earlier model discussed in Chapter V. The estimation of risk parameters a and b with the help of maximum likelihood method, however, involves voluminous calculations. Such a difficulty was also realized by Fix and Neyman (1951) in their stochastic model of recovery, relapse, death and loss of cancer patients. The estimation of daily gross malaria incidence and recovery rates, thus, did not seem feasible by the model formulated in Section 6.1.

The alternative approach detailed in Section 6.2 provides a model from which daily gross malaria rates can easily be calculated. This model which assumes only one transition from 'positive' state to 'negative' state or vice-versa between (0, t) is simple, practicable and involves less calculations for the estimation of different parametric values. The approach employed for the formulation of the model significantly differs from that considered in Section 6.1 or Chapter V. However, like other models, it is also based on a few assumptions. Main assumptions are that, parallel to the force of malaria infection, there are two other forces - reversible force and force of 'lost to follow-up' of cases, simultaneously acting at a point of time in the population, and that 'negatives' and 'positives' are transferred to rest other two states at the constant rates. These assumptions seem quite relevant as the rates have been calculated for 'per day' and the period of one day is sufficiently small in this respect.

The daily gross rates of malaria parasite indicated that in the population studied, about 11 males and 6 females per 10,000 population got fresh malaria infection including relapse, if any, per day.

Similarly, gross conversion rates per day were 32/1,000 for males against 20/1,000 for females. This indicated that about 32 'positive' males and 20 'positive' females per 1,000 population got rid of malaria infection per day. However, since malaria parasite positivity was based only on pat-ent parasitaemia, the observed recovery rates include lapses, if any, in the examination of blood for malaria parasites and natural latency.

It is easy to see from numerical illustrations, particularly from those shown in Table 6.4, that model gives appreciable results in respect of monthly gross malaria transition probabilities from one state to the other. The predicted values of such probabilities are exactly the same as were observed actually. The results on 'expected duration of positive episode' showed interesting results. Such results indicate that the duration of positive episode' has been of 32 days for males and 49 days for females. This indicated that males and females of the area continued to suffer from malaria, on an average, for a period of 32 days and 49 days respectively.

Like Chapter V, the equilibrium parasite rates were also estimated utilizing daily gross malaria parasite incidence and recovery rates.

The percentage value of $\hat{a}_1/(\hat{a}_1 + \hat{b}_1)$ gave such rates (Molineaux and Gramiccia, 1980). The overall expected equilibrium parasite rate was estimated to be about 3% (3.02%) against about 4% (3.62%) actually observed. This difference could, probably, have been because of gross rates utilized in the estimation and also due to the effect of a few factors, like age and species of parasites, which could not be taken into consideration while making such estimations.

The formulated model would provide more precise results if applied to the homogeneous populations, particularly to those defined by age, sex and area. In view of very few malaria positive cases, studied population was not classified by age, besides sex. Thus, our population, in fact, can not be taken to be strictly homogeneous. The deviated results, if any, might probably have been because of this reason, to a great extent.

The model can be applied to study epidemiological situations of malaria in an area, in studying the impact of malaria control programmes and to study the mechanism of the transmission of disease etc. It can easily be applied to other diseases almost behaving like malaria where

consideration of reversible force and the force of 'lost to follow-up' in the mechanism of transition from one state to the other are possible.

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CHAPTER VII

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA — CONSIDERATION OF DIFFERENT MALARIA SPECIES

ESTIMATION OF DAILY MALARIA PARASITE INCIDENCE AND RECOVERY RATES AND TRANSITION PROBABILITIES IN GENERAL POPULATION FROM LONGITUDINAL DATA - CONSIDERATION OF DIFFERENT MALARIA SPECIES.

In the previous Sections, attempts have been made to suggest stochastic models to estimate daily malaria parasite incidence and recovery rates in the two different situations - (i) when individuals of the population studied initially are covered, in toto, during subsequent follow-ups and (ii) when a few individuals are 'lost to follow-up' in latter case. These models, however, do not allow one to estimate malaria transition rates specified for its different species when the risk of 'lost to follow-up' is present or otherwise.

As indicated earlier, malaria is caused by 4 species - P.vivax, P.falciparum, P.malariae and P.ovale. Of these, P.vivax is the most rife infection followed by P.falciparum and then others. In our country, P.vivax has been found to be responsible for 65-69%, P.falciparum for 25-30% and mixed infections for 4-8% of total malaria positive cases (Park and Park, 1977).

Distribution of P.malariae is considerably restricted and is known to be responsible only for about 1% of total cases. P.ovale has, so far, not been detected in India though, it is well prevalent in Africa and Vietnam (W.H.O., 1970). Recurrences are seen in all types of malaria; some species may cause prolonged low level parasitaemia and the infection in a few types of malaria may even persist for many years.

Estimation of malaria transition rates by species is important in studying their epidemiological patterns; this is necessary as different species of malaria have different epidemiological features. Here, a probability model with 7 states is formulated to estimate daily malaria transition rates. The model allows one to assess daily malaria parasite incidence and recovery rates by species from longitudinal data in the presence of the risk of 'lost to follow-up' of cases. However, applicability of the model is not illustrated in view of non-availability of desired type of data.

7.1 ASSUMPTIONS.

Following assumptions have been made.

(i) All members of the population are susceptible to malaria infection and that, the infection

(ii) Individuals of the population contact the infectious agent independently and equally.

(iii) The transitions from one state, say S_i to another state S_j may take place at any instant between two consequtive surveys.

(iv) Only one type of transition, either from 'negative' to 'positive' or from 'positive' to 'negative' etc., for each species is possible in a unit of time.

(v) The probability of transfer from state S_i at time t_1 (say) to state S_j at time t_2 (say) can be represented by the conditional probability $p_{ij}(t_2 - t_1)$.

7.2 THE MODEL.

Consider a population which is studied longitudinally for the purpose. An individual at any point of time during a given period may be negative or positive for any one or more malaria species etc. His status may be categorized in any one of the following 7 defined mutually exclusive states.

S_1 : Individual is free from malaria.

S_2 : Individual is positive for P.vivax only.

S_3 : Individual is positive for P.falciparum only.

FLOW CHART OF A MALARIA MODEL BASED ON MULTIPLE STATES-SHOWING POSTULATED NUMBER OF STATES AND POSSIBILITIES OF TRANSITIONS.

S.NO.	STATE
1.	FREE FROM MALARIA.
2.	POSITIVE FOR P. VIVAX ONLY
3.	POSITIVE FOR P. FALCIPARUM ONLY.
4.	POSITIVE FOR P. OVALE ONLY.
5.	POSITIVE FOR P. MALARIAE ONLY.
6.	POSITIVE FOR MIXED INFECTIONS.
7.	'LOST TO FOLLOW-UP' OR DEAD FROM CAUSES OTHER THAN MALARIA.

CONSIDERED TIME INTERVAL
$0 \ldots\ldots \tau \ldots\ldots t$

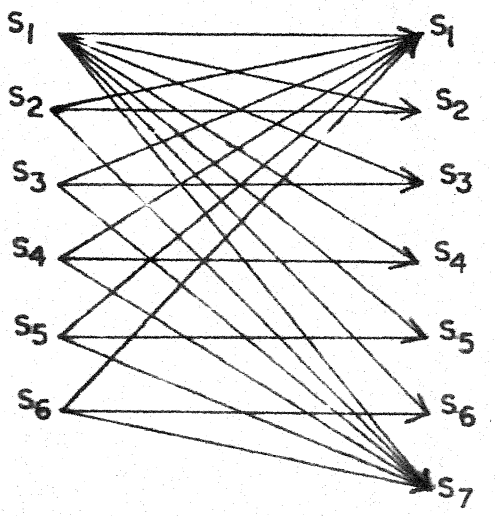


FIGURE 7·1

S_4 : Individual is positive for P.ovale only.

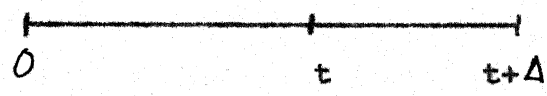
S_5 : Individual is positive for P.malariae only.

S_6 : Individual is positive for mixed malariae infections.

S_7 : Individual is 'lost to follow-up' as he moves away or is difficult to trace or dies of causes other than malaria in the presence or absence of malaria morbidity.

Now, on the basis of natural history of the disease, the transitions between different states can easily be outlined (Figure 7.1). An individual who is detected to be negative for malaria at the time of initial survey may remain negative till follow-up time or may become positive for any malaria species. He may be infected, at a time, with more than one malaria species. He may also be lost to follow-up because of many likely reasons, viz, - moved to some other place, refused to co-operate or dead. Similarly, a person found positive for malaria at initial survey may continue to suffer from malaria till the follow-up time or may become negative or may be lost to follow up. In other words, an individual initially in state S_1 may remain in S_1 till the time of his follow-up or leave S_1 and join anyone of the defined states - S_2, S_3, S_4, S_5, S_6 and S_7. Similarly, an individual initially in anyone of the states - S_2, S_3, S_4, S_5 and

S_6 may again remain there till the time of follow-up or leave original state and join state S_1 by way of recovery from malaria morbidity. He would join state S_7 if 'lost to follow-up'. States S_1 to S_6 are transient states while S_7 is the absorbing state since, once an individual entered in state S_7, he will remain there for ever. Further, in view of assumption (iv), inter-transitions between the states – S_2 to S_6 are not possible.



Consider 3 points 0 , t and $t+\Delta$, such that $0 < t < t+\Delta$, on the time axis. The Kolmogorov differential equation (Chiang, 1968) of the probability of a transfer from state S_i to state S_k during time interval (0, t) can be written as,

$$\frac{\partial}{\partial t} p_{ik}(0\ ,\ t) = \sum_{j=1} p_{ij}(0\ ,\ t)\ v_{jk}(t) \qquad \text{----------(1)}$$

Since the Morkov Process X(t) is homogeneous in time, intensity function $v_{ij}(t)$ will be independent time t. We further assume that the system is closed so that for every i, whatever may be t $\geq$ 0,

$$\sum_{j=1}^{7} p_{ij}(t) = 1, \qquad \text{for} \quad \begin{matrix} i = 1,2,.....6 \\ j = 1,2,.....7 \end{matrix}$$

$$\text{Or, } v_{ii} = -\sum_{j=1}^{6} v_{ij}, \qquad i = 1,2,.....6$$

The Kolmogorov differential equation (1) will, thus, be,

$$\frac{\partial}{\partial t} P_{ik}(t) = \sum_{j=1}^{7} P_{ij}(t)\, v_{jk} \qquad \text{----------(2)}$$

with initial conditions

$$P_{ik}(0) = 1 \text{ , for } i = k$$

and

$$P_{ik}(0) = 0 \text{ , for } i \neq k$$

The equation (2) can also be written in matrix form.

Let,

$$P(t) = \begin{bmatrix} P_{11}(t) & P_{12}(t) & \cdots\cdots & P_{17}(t) \\ P_{21}(t) & P_{22}(t) & \cdots\cdots & P_{27}(t) \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ P_{61}(t) & P_{62}(t) & \cdots\cdots & P_{67}(t) \end{bmatrix} \qquad \text{---------(3)}$$

be the transition probability matrix and

$$V = \begin{bmatrix} v_{11} & v_{12} & \cdots\cdots & v_{17} \\ v_{21} & v_{22} & \cdots\cdots & v_{27} \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ \cdots\cdots & \cdots\cdots & \cdots\cdots & \cdots\cdots \\ v_{61} & v_{62} & \cdots\cdots & v_{67} \end{bmatrix} \qquad \text{----------(4)}$$

be the intensity function matrix. Because of assumption (iv), the inter-transitions between the states S_2 to S_6 can not take place. The transition probability matrix P(t) and intensity function matrix V can, thus, be written as,

$$P(t) = \begin{bmatrix} p_{11}(t) & p_{12}(t) & p_{13}(t) & p_{14}(t) & p_{15}(t) & p_{16}(t) & p_{17}(t) \\ p_{21}(t) & p_{22}(t) & 0 & 0 & 0 & 0 & p_{27}(t) \\ p_{31}(t) & 0 & p_{33}(t) & 0 & 0 & 0 & p_{37}(t) \\ p_{41}(t) & 0 & 0 & p_{44}(t) & 0 & 0 & p_{47}(t) \\ p_{51}(t) & 0 & 0 & 0 & p_{55}(t) & 0 & p_{57}(t) \\ p_{61}(t) & 0 & 0 & 0 & 0 & p_{66}(t) & p_{67}(t) \end{bmatrix} \quad (5)$$

and,

$$V = \begin{bmatrix} v_{11} & v_{12} & v_{13} & v_{14} & v_{15} & v_{16} & v_{17} \\ v_{21} & v_{22} & 0 & 0 & 0 & 0 & v_{27} \\ v_{31} & 0 & v_{33} & 0 & 0 & 0 & v_{37} \\ v_{41} & 0 & 0 & v_{44} & 0 & 0 & v_{47} \\ v_{51} & 0 & 0 & 0 & v_{55} & 0 & v_{57} \\ v_{61} & 0 & 0 & 0 & 0 & v_{66} & v_{67} \end{bmatrix} \quad \text{--------(6)}$$

Then, the corresponding matrix equation will be,

$$D\,P(t) = P(t)V \qquad \text{----------(7)}$$

Where D is the diagonal matrix with the differentiation parameter operator $\frac{\partial}{\partial t}$ on the diagonal line.

Further, if we ignore the fact that P(t) and V are matrices, the equation (7) is an ordinary first order differential equation.

Therefore,

$$P(t) = e^{Vt} \text{ and } P(0) = I \qquad \text{----------(8)}$$

where I is the identity matrix.

Also,

$$e^{Vt} = \sum_{n=0}^{\infty} \frac{V^n t^n}{n!} \qquad \text{----------(9)}$$

The matrix series (9) converges uniformly in t (Doob, 1953 and Bellman, 1960).

Now, if we can estimate the intensity matrix V, we can easily evaluate transition matrix P(t). The estimate of V is based on a series, expansion of V in terms of P(t).

Let

$$P^*(t) = P(t) - I \qquad \text{----------(10)}$$

Then,

$$P(t) = P^*(t) + I = e^{Vt}$$

Or,

$$\text{Log } (P^*(t) + I) = Vt$$

Or,

$$Vt = P^*(t) - \frac{(P^*(t))^2}{2} + \frac{(P^*(t))^3}{3} - \frac{(P^*(t))^4}{4} + \ldots . \quad (11)$$

Thus, matrix V can now be estimated from equation (11).

7.3 ESTIMATION OF PARAMETER.

Let us consider a more general case than that considered in the previous Sections. Suppose that the population is studied longitudinally over time-period T by conducting various follow-ups at interval t, for $t \leq T$. As assumed earlier, t is sufficiently small to allow only one transition, either from positive to negative or from negative to positive for specific malaria species during two consecutive study timings.

Further, consider an individual having been taken in the study as an independent trial. After period t has elapsed, individual of the population can be classified into any one of the 7 defined mutually exclusive states - S_1, S_2, ... S_7. If the individual is dead or 'lost to follow-up', only then

the series of classification terminates at a specific follow-up time, otherwise the classification continues until the cut-off date.

The observed clinical path of the individuals would, thus, consist of a sequence of states given below.

$$S_{i_1}, S_{i_2}, S_{i_3} \ldots S_{i_k}, \text{ for } k = 1,2,\ldots\ldots 7.$$

Here S_{i_1} is the initial state and S_{i_2} is the state after period t has elapsed. Within period T, let follow-ups be done subsequently at different timings, say at times - t_1 , t_2 , ... t_k such that $t_1 < t_2 < t_3 < t_4 \ldots\ldots < t_k$. Because the difference between any two consecutive follow-ups is equal to t and, since process is homogeneous in time, the probabilities of the above sequence can be written as,

$$P_{i_1}, P_{i_1 i_2}(t), P_{i_2 i_3}(t), \ldots\ldots P_{i_{k-1}}{}_{k}(t).$$

If N_i is the number of individuals entering the state S_i and N_{ij} be the number of transitions from state S_i to S_j, the likelihood of clinical path of individuals will be

$$L = \prod_{i=1}^{k} \prod_{j=1}^{k} (p_i)^{N_i} \left[p_{ij}(t)\right]^{N_{ij}}$$

$$= \prod_{i=1}^{k} \left[(p_i)^{N_i} \prod_{j=1}^{k} p_{ij}(t)^{N_{ij}}\right] \text{ ----------(12)}$$

Here, we define that,

$$p_i = 1, \text{ for } N_i = 0, \; i=1,2,.....6$$

and

$$p_{ij}(t) = 1 \text{ for } N_{ij} = 0 \quad \begin{matrix} i=1,2,.....6 \\ j=1,2,.....7 \end{matrix}$$

Taking logarithm on both the sides of equation (12) and differentiating it with respect to $p_{ij}(t)$ for fixed i and for different j = 1,2,.....7, various equations, viz.,

$$\frac{\partial \log L}{\partial p_{i2}(t)} = \frac{\partial \log L}{\partial p_{i3}(t)} = ... = \frac{\partial \log L}{\partial p_{i7}(t)} = 0.$$

can be derived. After rearranging, such equations are,

$$p_{i2}(t)\left[N_i - \sum_{j=3}^{7} N_{ij}\right] + N_{i2}\left[\sum_{j=3}^{7} p_{ij}(t)\right] = N_{i2}$$

$$p_{i2}(t)\, N_{i3} + p_{i3}(t)\left[N_i - N_{i2} - \sum_{j=4}^{7} N_{ij}\right] + N_{i3} \sum_{j=4}^{7} p_{ij}(t) = N_{i3} \qquad \text{---(13)}$$

. . . . . .

. . . . . .

$$p_{i2}(t)\, N_{i7} + p_{i3}(t)\, N_{i7} + \ldots\ldots + p_{i6}(t)\, N_{i7} + p_{i7}(t)\left[N_i - \sum_{j=2}^{6} N_{ij}\right] = N_{i7}$$

Solution of equations (13) provides maximum likelihood estimate to $p_{i1}(t)$, $p_{i2}(t)$ ..... $p_{i7}(t)$ as given below.

$$\hat{p}_{ij}(t) = \frac{N_{ij}}{N_{i1}+N_{i2}+\ldots+N_{i7}} \text{ , for } i=1,2,\ldots.6$$

Since,

$$N_{i1} + N_{i2} + \ldots\ldots + N_{i7} = N_i$$

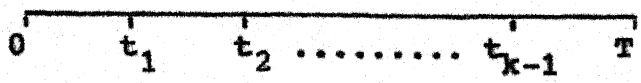
$$\hat{p}_{ij}(t) = \frac{N_{ij}}{N_i} \text{ , for } \begin{matrix} i=1,2,\ldots\ldots 6 \\ j=1,2,\ldots\ldots 7. \end{matrix}$$

Estimation of transition probabilities for a large period.

In morbidity studies, the incidence and recovery rates of a disease/condition are always dependent upon time period considered. In studies like malaria, when considered time period is relatively large, the precise assessment of these rates for entire period on the basis of only two surveys – one in the beginning and the other in the end, may not be possible; the reason being that an individual who is initially free from malaria may suffer from malaria many times within this period and at the end, he may become free again from it. The accurate estimation of above malaria rates is possible only when more than one follow-ups are done at suitable intervals. One way to study such rates is to carry-out a few surveys at suitable time points considering different sub-periods, work-out transition probabilities for each sub-period and then join these transition probabilities of various sub-periods to get desired malaria rates for the large considered period.

The transition probability matrix P(T) for the large considered period, say (0,T) can be worked-out in terms of transition matrix of different sub-periods

in the following way. Malaria transition rates within the period (0,T) can be studied by conducting only one, two, three, ... and k follow-ups.



We can write transition probability matrix for first period $(0, t_1)$ as $P_1(t_1)$, for second period (t_1,t_2) as $P_2(t_2-t_1)$ and so on. Following Chapman-Kolmogorov equation (Parzen, 1964).

We have,

$$
\begin{array}{ll}
P_1(t_1) & 0 \leq T \leq t_1 \\
P_1(t_1)\ P_2(T-t_1) & 0 \leq T \leq t_2 \\
P_1(t_1)\ P_2(t_2-t_1)\ P_3(T-t_2) & 0 \leq T \leq t_3 \qquad \text{---(14)} \\
\cdots\cdots\cdots\cdots\cdots\cdots & \\
\cdots\cdots\cdots\cdots\cdots\cdots & \\
P_1(t_1)\ P_2(t_2-t_1)\ldots P_k(T-t_{k-1}) & 0 \leq T \leq t_k
\end{array}
$$

Since, the difference between any two consecutive timing of the surveys is same and equal to t, equations (14) can be re-written as,

$$P(T) = \begin{vmatrix} P_1(t) & 0 \leq T \leq t_1 \\ P_1(t)\ P_2(t) & 0 \leq T \leq t_2 \\ P_1(t)\ P_2(t)\ P_3(t) & 0 \leq T \leq t_3 \\ \cdots\cdots\cdots & \cdots\cdots \\ \cdots\cdots\cdots & \cdots\cdots \\ P_1(t)\ P_2(t)\ \ldots\ldots P_k(t) & 0 \leq T \leq t_k \end{vmatrix} \quad \text{----(15)}$$

If $V_1, V_2, \ldots\ldots V_k$ be the intensity function matrices for first sub-period $(0, t_1)$, second sub-period (t_1, t_2) and so on, then equations (15) can also be expressed in terms of $V_1, V_2, V_3 \ldots\ldots V_k$. From (8), we have,

$$P(T) = \begin{vmatrix} I+V_1t+V_1^2t^2\cdot\frac{1}{2} + V_1^3t^3\cdot\frac{1}{2} + \ldots\ldots\ldots\ldots & 0 \leq T \leq t_1 \\ I+(V_1+V_2)t+(V_1+V_2)^2t^2\cdot\frac{1}{2} + \ldots\ldots\ldots & 0 \leq T \leq t_2 \\ I+(V_1+V_2+V_3)t+(V_1+V_2+V_3)^2t^2\cdot\frac{1}{2} + \ldots\ldots & 0 \leq T \leq t_3 \\ \cdots\cdots\cdots\cdots\cdots\cdots & \cdots\cdots \\ \cdots\cdots\cdots\cdots\cdots\cdots & \cdots\cdots \\ I+(V_1+\ldots\ldots V_k)t+(V_1+\ldots\ldots V_k)^2t^2\cdot\frac{1}{2} + \ldots\ldots & 0 \leq T \leq t_k \end{vmatrix} \quad \text{(16)}$$

The transition probabilities from one state to the other can now be studied for different sub-periods and then, they can be combined by using equations given in (15) or (16) according to the number of follow-ups considered during (0, T). The malaria parasite incidence and recovery rates for specific species for the entire time period T can ultimately be worked-out.

DISCUSSION.

In malaria, since the epidemiological features of its different species are often different, the values of various important epidemiological parameters should be worked-out for specific species separately. The models discussed in Chapters V and VI do not provide formulae for estimation of malaria transition rates, specified for different species either when risk of 'lost to follow-up' of cases is present or otherwise. The present model allows one to estimate species - specific daily malaria parasite incidence and recovery rates and transition probabilities in the presence of risk of 'lost to follow-up' of cases in any homogeneous population. The model is simple and practicable; the estimation of intensity function matrix V is also quite easy.

Since the available literature on the subject failed to provide data of desired nature, a door-to-door longitudinal study on malaria was carried-out (see, Chapter VIII) in a rural community of Jhansi district (U.P.) to obtain relevant data. However, total positive cases of malaria observed were so small that the application of the model after classifying them into different species for the two sexes separately did not seem practicable. Furthermore, our study on malaria showed positive cases belonging to two species only, viz., - P.vivax and P.falciparum, and cases belonging to rest other species including mixed were not all observed. In such a situation, the applicability and relative suitability of the model with the help of numerical illustrations could not be brought-forth.

It is, however, hoped that the evolved model would provide satisfactory results if relevant data pertaining to a homogeneous population are available. It is also expected that the model would be of great help to the epidemiologists, malariologists and to many other health personnels engaged in the malaria control programmes in studying species - specific epidemiological features of malaria and in choosing optimum strategy for its control.

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CHAPTER VIII

DATA SOURCE AND METHODS OF SURVEY

DATA SOURCE AND METHODS OF SURVEY

One of the important reasons for considerably lesser number of mathematical models available in different areas of malariology is, probably, the lack of relevant data. Under such situations, applicability, utility and relative suitability of some of the models, developed so far, for malariometric data are usually not illustrated. No doubt, a good number of studies on malaria are available, however, they mostly are either cross-sectional or based on hospital records providing no proper details on transition behaviour of the disease. Malariometric data from follow-up studies are rarely available. In longitudinal studies on diseases like malaria, groups of individuals are observed continuously for a specified period of time by conducting regular follow-ups at suitable intervals and as such, they are notoriously difficult to undertake. In India, hardly any study is available where epidemiological features of the disease have been studied by undertaking regular follow-ups. Since relevant data to illustrate applications of stochastic models, evolved in earlier Chapters were not available in published literature, a longitudinal

survey in a rural community of Jhansi district (U.P.) was carried-out by door-to-door visits. The details of methods of survey, population coverage and characteristics of the population studied etc are given here.

8.1 AREA AND POPULATION.

A door-to-door follow-up investigation on malaria was carried-out in a rural community, consisting of two villages, namely Pichhore and Digara, situated in the neighbourhood of M.L.B. Medical College, Jhansi (U.P.). This rural community, according to a survey conducted by the Department of Social and Preventive Medicine, M.L.B. Medical College, Jhansi (U.P.) a few months earlier had a population of 1,830 individuals in 278 families. Total population of these two villages was considered for the purpose and no efforts were made to apply any of the available sampling techniques and thus, to cover larger area in view of the limited facilities and time available.

8.2 METEREOLOGICAL CONDITIONS.

Malaria is a seasonal disease with definite monthly fluctuations. The transmission of the disease

usually varies from one region to the other and, at times, in the same region with time. Such variations in the level of transmission are determined by a variety of factors. Metereological conditions, such as - maximum and minimum temperatures, relative humidity and rainfall - are one of the important such factors which influence vector density, development of the sexual cycle in the mosquitoe-vector and longevity of mosquitoe-vector to allow sexual cycle to be completed.

District Jhansi, in a rural community of which the present study was undertaken, has a hot and dry climate. Metereological data of the district (Verma et al, 1977), indicate that the area has (i) mean monthly maximum temperature ranging from 24.1°C in the month of January to 42.6°C in the month of May, (ii) mean monthly minimum temperature from 9.2°C in the month of January to 29.3°C in the month of June, (iii) mean monthly relative humidity (at 0830 hrs.) ranging from 26% in the month of May to 84% in the month of November and (iv) mean monthly rainfall ranging from 2.7 mm. in the month of April to 309.1 mm. in the month of August.

8.3 MALARIA CONTROL OPERATIONS.

The area has been continuously covered with a residual insecticidal spray by N.M.E.P. unit Jhansi (U.P.) under National Malaria Eradication Programme since the year 1959 with two rounds of D.D.T. each year upto the year 1972. However, afterwards, the area received 3 rounds of B.H.C.(50%) each year (Srivastava et al, 1975). In 1980, when present longitudinal survey was carried-out, there were 3 rounds of B.H.C. (50%).

8.4 METHODS OF SURVEY.

The survey was carried-out by a team, headed by the author, including one demonstrator (medical), two interns (medical) and two lady social workers of the Department of Social and Preventive Medicine, M.L.B. Medical College, Jhansi, U.P. (where the author is presently employed). The team, for the purpose of the survey, visited every family of the two villages between 9.00 a.m. and 1.00 p.m. on each working day, and available persons were contacted for the purpose. During the survey, people of the area were first told about the objective of our visit and were then motivated by the team, particularly by social workers to give a few drops of blood for preparation of blood smears. Thick and thin blood smears were prepared for each individual who could be motivated.

Population of the area was studied longitudinally conducting, besides initial survey, regular follow-ups at the average time interval of 4 ± 8 weeks. However, because of limited time and facilities available, malaria situations of the area were studied by carrying-out only 3 surveys - one initial survey and two consecutive follow-ups. In order to have sufficient number of malaria cases, surveys were conducted during transmission season of the malaria. The work of data collection in the initial survey was started on August 15, 1980 and last follow-up ended on November 15, 1980. Thus, the observations on malaria situations of the area are based on a period of about 3 months only.

During the course of data collection, intensive efforts were made to cover every individual of the population. In the initial survey, an attempt was made to cover the maximum number of individuals. Those not available or refusing to cooperate at the time of first visit were contacted again for the purpose. Individuals, studied initially were treated to be the sampled - population for subsequent follow-up and only those covered in first follow-up were studied in second follow-up. No effort was made to study

those cases in the consecutive follow-ups who either had refused to co-operate or were not available at the time of prior visits.

In order to attain good coverage, individuals of the area were treated for minor ailments, if any. Sick people were given basic drugs (not anti-malarial drugs) at the time of the survey. The serious cases, if any, were advised admission in the nearby Medical College hospital. In order to study natural recovery rates in the area, as far as possible, anti-malaria drugs such as - Chloroquine and Camoquin etc were not given to the persons showing symptoms of fever at the time of first two surveys. At the time of third survey, however, fever cases were given presumptive treatment and those found positive for malaria parasites were given radical treatment.

In each survey, information in respect of every individual was recorded on a schedule developed for the purpose (appendix). This schedule was pre-tested in about 10 families of the village Pichhore, situated in the vicinity of Medical College, Jhansi (U.P.) and later, modified for anomalies, if any. In view of limited facilities available, neither a large population could be considered nor any sampling technique could be used after determining the size of the sample statistically for specified precision.

Ages of individuals particularly, of school children and adults were assessed through personal and closed interviews; however, for pre-school children, parents particularly, mothers were enquired for the purpose. Ages of infants were assessed by developing a local calender of important events of the area and then by interviewing respective mothers.

Socio-economic status of the individuals was recorded based on the social classification of Indian families, recently broughtforth by us (Srivastava et al, 1980 a) and used elsewhere (Srivastava, 1980 b). Social classification of the families, here too, is based on mean monthly per capita income, as recommended by Prasad (1970). Our criterion on social classification is, in fact, an improvement over that of Prasad (1970) and is given as under :

Social Class	Mean monthly per capita income
I	Rs. 600/- and above.
II	Rs. 300/- — Rs. 599/-
III	Rs. 140/- — Rs. 299/-
IV	Rs. 60/- — Rs. 139/-
V	Below Rs. 60/-

Prasad's criterion (1970) was not used as it is based on the value of Indian rupee for the year 1970 or prior to it and therefore, has now become obsolete in view of considerable decline in the purchasing power of rupee during recent decade.

8.5 EXAMINATION OF BLOOD SMEARS.

During the course of the survey, on an average, about 50 thick and thin blood slides were prepared daily by the survey team. These were stained with the Leishman's stain in the laboratory of our Department and then examined by a trained Laboratory Technician, appointed full time therein. As far as possible, negative slides were re-examined by one of the senior staff members (medical) to check the possible lapses, if any, in their earlier examination.

8.6 POPULATION COVERAGE.

Area studied had a population of 1,830 individuals with 982 (53.7%) males and 848 (46.3%) females. Distribution of the total population in the two villages and its coverage in the initial survey by age and sex has been given in Table 8.1.

Data indicate that coverage in the initial survey has been only 51.20%. It was higher for

TABLE 8.1

Population coverage (%) at initial survey by age and sex.

Age-group (year)	TOTAL POPULATION						POPULATION STUDIED INITIALLY					
	Male		Female		Total		Male		Female		Total	
	No.	%	No.	%	No.	%	No.	Coverage (%)	No.	Coverage (%)	No.	Coverage (%)
Below 1	16	1.63	13	1.53	29	1.58	10	62.50	10	76.92	20	68.97
1 - 4	94	9.58	86	10.14	180	9.84	72	78.26	80	93.02	152	84.44
5 - 14	326	33.20	261	30.78	587	32.08	169	51.84	143	54.79	312	53.15
15 - 24	175	17.82	131	15.46	306	16.78	73	41.71	51	38.93	124	40.52
25 - 34	114	11.61	126	14.85	240	13.11	44	38.60	82	65.08	126	52.50
35 - 44	117	11.91	98	11.56	215	11.75	40	34.19	51	52.04	91	42.33
45 - 54	75	7.63	57	6.72	132	7.21	28	37.33	27	47.37	55	41.67
55 & over	15	6.62	76	8.96	141	7.70	21	32.31	36	47.37	57	40.43
All ages	982	100.00	848	100.00	1,830	100.00	457	46.54	480	56.60	937	51.20

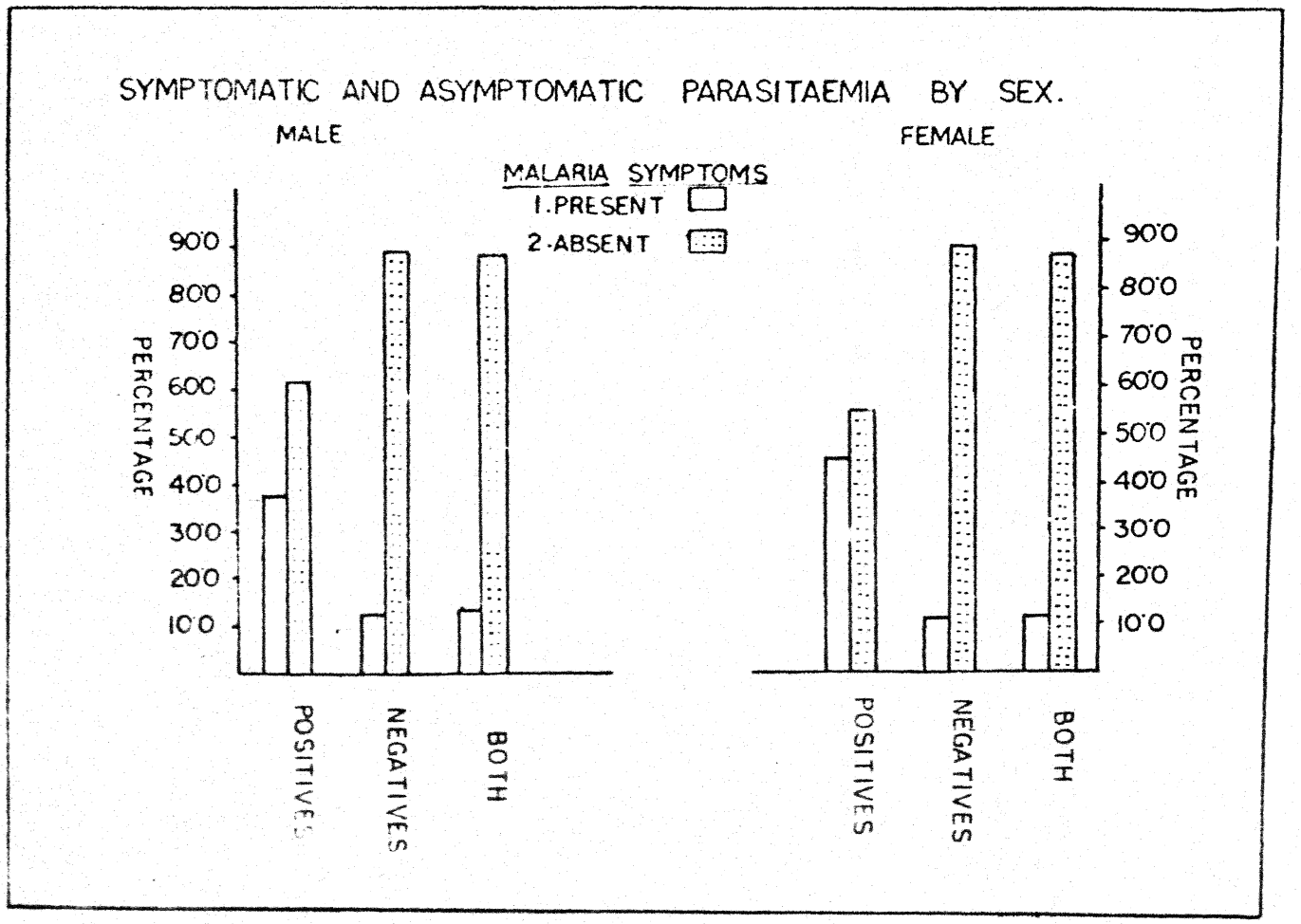
SYMPTOMATIC AND ASYMPTOMATIC PARASITAEMIA BY SEX.
MALE
FEMALE
MALARIA SYMPTOMS
1.PRESENT
2.ABSENT
PERCENTAGE
90·0
80·0
70·0
60·0
50·0
40·0
30·0
20·0
10·0
POSITIVES
NEGATIVES
BOTH

FIGURE 8·1

females (56.60%) than males (46.64%). Coverage was relatively better for persons of younger ages than those who belonged to the older age-groups. As indicated earlier, only 937 individuals could be studied further at the time of first follow-up as only these individuals had been studied for the purpose in the initial survey.

8.7 RESULTS OF THE SURVEY.

Malaria parasite rates by presence or otherwise of malaria symptoms and by various socio-economic and demographic characteristics of the individuals were studied; the relevant findings in these respects are given as under.

8.7.1 Symptomatic and asymptomatic malaria

Data on symptomatic and asymptomatic parasitaemia, observed in the initial survey are given in Table 8.2. Analysis indicates that, out of 937 individuals studied, only 32 cases – 21 males and 11 females – were detected to be positive for malaria. In males, about 62% individuals showed asymptomatic parasitaemia against about 55% in case of females (Figure 8.1). About 12% males and 10% females were observed to be negative for malaria though, they had malaria symptoms,

TABLE 8.2

Symptomatic and asymptomatic parasitaemia observed in the initial survey.

Result of blood examination.	MALE					FEMALE				
	Malaria symptoms present or not.					Malaria symptoms present or not.				
	Yes		No		Total	Yes		No		Total
	No.	%	No.	%		No.	%	No.	%	
Positive for malaria	8	38.09	13	61.91	21	5	45.46	6	54.54	11
Negative for malaria	51	11.70	385	88,30	436	49	10.45	420	89.55	469
Total	59	12.91	398	87.09	457	54	11.25	426	88.75	480

such as – fever with chills and rigors etc. Proportions of persons having asymptomatic parasitaemia did not differ significantly in two sexes ($t = 0.3690$, $P > 0.5$).

8.7.2 Malaria and age

Malaria parasite rates, observed in the initial survey by age and sex are given in Table 8.3. Data indicate that, though some infants were studied for malaria, no one was found to be positive. However, malaria was well prevalent in children and adult population. Malaria parasite rate was about 4% in children against about 3% in adults; the difference being statistically insignificant ($t = 1.0215$, $P > 0.05$).

8.7.3 Malaria and sex

Analysis of data shown in Table 8.3 further provides interesting results on sex-specific malaria parasite rates. Males, by and large, had a relatively higher rate (4.67%) than females (2.35%). Such rates were higher for males than females for children as well as for adults. However, this difference too, could not reach the level of statistical significance ($t = 1.4970$, $P > 0.05$).

TABLE 8.3

Age and sex-specific malaria parasite rates (%) in the initial survey.

Age-group (year)	Type of population	MALE			FEMALE			TOTAL		
		Examined	Positive for malaria	Parasite rate (%)	Examined	Positive for malaria	Parasite rate (%)	Examined	Positive for malaria	Parasite rate (%)
Below 1	Infants	10	Nil	Nil	10	Nil	Nil	20	Nil	Nil
1 - 14	Children	241	11	4.56	223	8	3.58	464	19	4.09
15 & above	Adults	206	10	4.85	247	3	1.21	453	13	2.87
Total		457	21	4.60	480	11	2.29	937	32	3.42

8.7.4 Malaria-species

Table 8.4 provides data on malaria parasite rates by age, sex and malaria-species. It may be seen that only two species - P.vivax and P.falciparum were detected. Out of 32 positive cases observed in the area during initial survey, only 3 were of P.falciparum and rest 29 were of P.vivax, indicating predominance of the latter in the area. Parasite rates by species were also somewhat higher for males than females, however for age, they did not show any specific pattern.

8.7.5 Malaria and literacy level

Malaria parasite rates by literacy status of the individuals are given in Table 8.5 for the two sexes separately. Analysis indicates that malaria was well prevalent in illiterates or in those educated upto Junior high school. On the other hand, persons with higher education showed no evidence of parasitaemia.

8.7.6 Malaria and occupation

Association of malaria parasite rates with the occupation of the individuals, if any, has also been studied (Table 8.6). The rates differred considerably

TABLE 8.4

Malaria parasite rates (%) by species for males and females separately.

Age-group (year)	MALE							FEMALE						
	Number studied	SPECIES* OF PARASITE						Number studied	SPECIES* OF PARASITE					
		P.vivax		P.falciparum		Total			P.vivax		P.falciparum		Total	
		No.	Parasite rate (%)	No.	Parasite rate (%)	No.	Parasite rate (%)		No.	Parasite rate (%)	No.	Parasite rate (%)	No.	Parasite rate (%)
Below 1	10	Nil	Nil	Nil	Nil	Nil	Nil	10	Nil	Nil	Nil	Nil	Nil	Nil
1 - 14	241	10	4.15	1	0.41	11	4.56	223	7	3.14	1	0.45	8	3.59
15 & above	206	9	4.37	1	0.49	10	4.85	247	3	1.21	Nil	Nil	3	1.21
Total	457	19	4.16	2	0.44	21	4.60	480	10	2.08	1	0.21	11	2.29

* Only two species of malaria, namely P.vivax and P.falciparum were observed.

TABLE 8.5

Malaria parasite rates (%) by literacy status and sex in the initial survey.

Literacy status	MALE			FEMALE			TOTAL		
	Examined	Positive for malaria	Parasite rate (%)	Examined	Positive for malaria	Parasite rate (%)	Examined	Positive for malaria	Parasite rate (%)
Illiterate	235	13	4.41	438	9	2.05	733	22	3.00
Just literate	62	2	3.23	25	1	4.00	87	3	3.45
Primary	56	4	7.14	10	Nil	Nil	66	4	6.06
Junior H.S.	30	2	6.67	6	1	16.67	36	3	8.33
High School	9	Nil	Nil	1	Nil	Nil	10	Nil	Nil
Intermediate	3	Nil	Nil	Nil	Nil	Nil	3	Nil	Nil
Graduate & more	2	Nil	Nil	Nil	Nil	Nil	2	Nil	Nil
Total	457	21	4.60	480	11	2.29	937	32	3.42

TABLE 8.6

Malaria parasite rates (%) by occupation in the initial survey.

Occupation	Examined	Positive for malaria	Parasite rate (%)
Agriculture/ Cultivation	106	5	4.72
Business	1	Nil	Nil
Labour	61	4	6.56
Service	17	Nil	Nil
Housework/ Housewife	249	5	2.01
Skilled profession	11	Nil	Nil
Others	492	18	3.66
Total	937	32	3.42

for different occupations. Highest rate was observed for labourers (6.56%), followed by agriculturists/ cultivators (4.72%). As against this, servicemen or those engaged in skilled professions did not show any evidence of parasitaemia.

8.7.7 Malaria and socio-economic status

In order to study the pattern of malaria parasite rates vis-a-vis socio-economic status of the individuals, social classes of individuals were worked-out as per our criterion (Srivastava et al, 1980 a). Malaria parasite rates were then studied for different social classes (Table 8.7).

TABLE 8.7

Malaria parasite rates (%) by social status* in the initial survey.

Social Class**	Examined	Positive for malaria	Parasite rate (%)
III	4	Nil	Nil
IV	103	2	1.94
V	830	30	3.61
Total	937	32	3.42

* Social status was categorized in different social classes according to the criterion, broughtforth by us (Srivastava et al, 1980 a).

** No respondent came from Social classes I and II.

It may be seen that people of the area, by and large, were poor. Majority of the studied persons (88.58%) belonged to social class V, followed by social class IV (10.99%) and then social class III (0.43%). No person came from social classes I and II. A relatively higher parasite rate (3.61%) was observed for those belonging to social class V as against about 2% for social class IV.

8.7.8 Transition patterns of malaria

As indicated earlier, besides initial survey two subsequent follow-ups at an average,interval of 4 weeks were also conducted. Transition patterns of malaria during the two follow-ups and for both the sexes have been given separately in Tables 8.8 and 8.9.

It may be seen from the data that, for the two sexes during the two follow-ups, majority of persons who had been studied earlier for the purpose could not be contacted because they either did not co-operate or were not available at the time of our visits and thus, were 'lost to follow-up'. In spite of the best efforts by the survey team, only this much proportion of persons could be studied.

For males, data indicate that, out of 21 cases which had been found positive initially,

TABLE 8.8

Patterns of malaria transitions between initial survey (Survey I) and first follow-up (Survey II) and between first follow-up (Survey II) and second follow-up (Survey III) in males.

TRANSITION PATTERNS OF MALARIA BETWEEN SURVEYS												
SURVEYS I AND II						SURVEYS II AND III					
Survey I			Survey II			Survey II			Survey III		
Result of blood examination	No.	%	Result of blood examination	No.	%	Result of blood examination	No.	%	Result of blood examination	No.	%
Positive	21	4.60	Positive	5	23.81	Positive	8	5.26	Positive	Nil	Nil
			Negative	3	14.29				Negative	4	50.00
			Lost to follow-up	13	61.90				Lost to follow-up	4	50.00
			Total	21	100.00				Total	8	100.00
Negative	436	95.40	Positive	3	0.69	Negative	144	94.74	Positive	2	1.39
			Negative	141	32.33				Negative	69	47.92
			Lost to follow-up	292	66.98				Lost to follow-up	73	50.69
			Total	436	100.00				Total	144	100.00
Total	457	100.00				Total	152	100.00			

TABLE 8.9

Patterns of malaria transitions between initial survey (Survey I) and first follow-up (Survey II) and between first follow-up (Survey II) and second follow-up (Survey III) in females.

TRANSITION PATTERNS OF MALARIA BETWEEN SURVEYS									
SURVEYS I AND II						SURVEYS II AND III			
Survey I			Survey II			Survey II			Survey III		
Result of blood examination	No.	%	Result of blood examination	No.	%	Result of blood examination	No.	%	Result of blood examination	No.	%
Positive	11	2.29	Positive	4	36.36	Positive	7	3.76	Positive	2	28.57
			Negative	1	9.09				Negative	3	42.86
			Lost to follow-up	6	54.55				Lost to follow-up	2	28.57
			Total	11	100.00				Total	7	100.00
Negative	469	97.71	Positive	3	0.64	Negative	179	100.00	Positive	1	0.56
			Negative	179	38.16				Negative	81	45.25
			Lost to follow-up	287	61.20				Lost to follow-up	97	54.19
			Total	469	100.00				Total	179	100.00
Total	480	100.00				Total	186	100.00			

only 3 (14.29%) recovered and 5 continued to remain in the same state. At second time, out of 8 such cases studied, 4 (50.00%) recovered and none remained in the same state. Similarly, out of 436 negatives studied, 3 (0.69%) became positive and 141 (32.33%) remained in the same state. For second time, however, out of 144 such cases, only 2 became positive and 69 (47.92%) continued to remain in their original state.

For females, similarly, out of 11 persons, who were detected positive initially, only 1 (9.09%) recovered and 4 (36.36%) continued to be in the same state. For those such cases, who were studied at second time, only 28.57% remained positive and 42.86% became negative. Similarly, out of 469 negatives studied, only 3 (0.64%) became positive and 179 remained in the same state. Out of 179 such cases studied at second time, 81 (45.25%) remained in the same state and only 1 (0.56%) became positive.

8.7.9 Monthly malaria transition rates

Though, the two subsequent follow-ups, were conducted at a difference of about 28 days, it was later observed that the average difference between two study timings per person was of about 30 days.

Thus, the two transition rates, studied during two consecutive surveys would refer to the monthly rates.

Such rates have been shown in Table 8.10. Since 'lost to follow-up' of cases have been ignored for the analysis, the observed rates may be termed as monthly 'net rates'.

Analysis indicates a monthly negative-to-positive transition rate of about 2.0% (1.88%) and positive-to-negative rate of 50.0%. For males, these rates were 2.33% and 58.33% respectively, against 1.52% and 40.0% respectively, in case of females. No statistically significant differences were observed between males and females for negative-to-positive ($t = 0.6483$, $P > 0.05$) and for positive-to-negative ($t = 0.8407$, $P > 0.05$) transition rates.

8.8 DISCUSSION.

As indicated earlier, malaria in India, is one of the worst scourges. Transmission dynamics of the disease need to be studied in order to understand the extent of problem, effect of control/preventive measures and to get data to study the applicability and relevance of mathematical models, if any.

TABLE 8.10

Monthly malaria transition rates* (%).

Sex	Type of cases studied	No. studied**	RESULT OF SUBSEQUENT BLOOD EXAMINATION		Monthly malaria transition rate (%)
			Remained positive/ negative	Became negative/ positive	
Male	Positive	12	5	7	58.33
	Negative	215	210	5	2.33
Female	Positive	10	6	4	40.00
	Negative	264	260	4	1.52
Total	Positive	22	11	11	50.00
	Negative	479	470	9	1.88

* Rates are based on the observations, made in two follow-ups (Surveys II and III).

** Cases 'lost to follow-up' are excluded.

Recently, it has been recommended (Molineaux and Gramiccia, 1980) that, in order to study malaria situations and its different associated aspects in depth, longitudinal studies on macro and micro levels should be undertaken, particularly, in the populations where scourge of malaria still poses a serious threat. The present investigation was carried-out in a small area to provide, inter alia, data on transmission patterns of the disease.

In the present follow-up investigation, coverage has been considerably low particularly, in the two follow-ups. In initial survey too, only about 51% persons of the total population could be studied. In fact, in the studies like present one where a few drops of blood are to be taken from individuals for examination, low coverage is unavoidable particularly, for rural populations of India. In such populations, people are often illiterate and poor, and in spite of using high motivational techniques, they are not easily prepared to provide a few drops of blood, probably because of the fear that, it would weaken them. In subsequent follow-ups, mostly people either did not co-operate/respond or were not available at the time of our visits owing to their outdoor activities

at the distant fields etc which ultimately, resulted in low coverage. Women of the area, by virtue of their indoor works, were more often available in their homes. Thus their coverage was higher than that of males.

During the course of this investigation, people suffering from minor ailments such as - diarrhoea, dysentery, fever, pains and minor injuries were provided basic drugs and those suffering from serious/fatal diseases were advised admissions in the nearby Medical College hospital. This was mainly done to gain faith of villagers and thus, to acquire desired coverage by way of their co-operation. It was realized that provision of such facilities helped considerably to enhance coverage in initial survey and in subsequent follow-ups.

Data indicate interestingly important results in respect of symptomatic and asymptomatic parasitaemia. Out of 32 positive cases detected in the initial survey, only 13 (40.62%) had malaria symptoms and rest about 59% did not have any symptom of malaria. This envisages that assessment on actual extent of malaria in a population cannot be made on the basis of blood slides collected from fever cases only.

Further, 100 cases who were found negative for malaria had one or the other symptoms. These cases, probably, had some ill-health conditions, other than malaria, having similar symptoms.

Association of malaria parasite rates were studied with some of the socio-demographic characteristics of the individuals. Such rates were relatively higher for males than females for different age-groups and malaria species. This could have probably been because of the fact that males often go for outdoor works near ponds, nullah and other malarious places without being well attired. Similar observations have been made in a study on malaria morbidity in a teaching hospital (Srivastava et al, 1976). However, the observed sex-difference was not statistically significant. Similar has been the case with age.

It was further observed that malaria parasite rates were higher in those who were illiterates, belonged to low socio-economic status and/or engaged in professions like agriculture and labour. To us, such observations seem to be obvious as poor and illiterate people usually live in huts/ kutchcha houses and keep cattles inside their homes,

thus, resulting in the presence of mosquitoe breeding places with them. In view of all this, they become more prone to suffer from malaria.

Study of transition of individuals from malaria positive state to malaria negative state or vice-versa during one-month period enabled us to work-out monthly malaria parasite transition rates. Both rates were relatively higher for males than females but these sex-differences were not statistically significant.

In malaria, immunity increases with age, resulting in somewhat lower susceptibility in older persons. As such, it is usually thought appropriate to study transition rates for persons belonging to different age and sex separately for different malaria species. Here, unfortunately, data did not allow us to categorize it further by age or species as positive cases were very small in number.

During the course of the surveys, anti-malaria drugs were not given to the fever cases in order to study natural recovery rates and actual malaria parasite incidence rates, as far as possible. However, possibility of taking such drugs by these cases from other sources cannot be ruled out.

Thus, the observed positive-to-negative transition rates may not be absolutely natural. Similarly, observed negative-to-positive transition rates are based on patent parasitaemia and include relapses, if any.

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CHAPTER IX

ESTIMATION OF LONGEVITY BENEFITS OF MALARIA ERADICATION IN INDIA

ESTIMATION OF LONGEVITY BENEFITS OF MALARIA ERADICATION IN INDIA

In recent years, there has been an increasing trend of both malaria positive cases and annual parasite rates (Dutta and Bhasin, 1979). In 1975 alone, 51,66,142 positive cases of malaria took place in the country and 99 deaths were reported from its major hospitals (N.M.E.P., 1975). By the end of 1974, 1,136 million people were at the risk to suffer from malaria (Srivastava et al, 1975); even today, hundreds of millions of people are still exposed to such risk. The tantalizing problem of malaria in the country has attracted health administrators and biostatisticians alike.

Despite the implimentation of National Malaria Eradication Programme (N.M.E.P.) since the year 1958 in the country, there has been a considerable under reporting in malaria positive cases each year. In fact, for variety of reasons, such as - non consideration of asymptomatic parasitaemia in the present strategy of malaria surveillance, slackness of malaria workers and their poor efficiencies in

blood slide collection from all fever cases and the limitations of pathological tests to produce evidences on parasite positivity, particularly in cases where parasite density in blood is very low (Pull and Grab, 1974) etc; the number of positive cases, officially reported represents only a small fraction of the actual number*. Similar is the case with malaria deaths; the available figures are based on hospital data and that too of only a few. In order to get the actual number of malaria cases or/and malaria deaths, at least grossly, the officially reported figures will have to be inflated considerably taking suitable assumptions on its reporting efficiency. A gross estimate of actual number of deaths due to malaria can then be made with the help of its observed case fatality rate.

It is rather difficult to estimate the longevity benefits of malaria eradication or additional years of life that would be saved by an individual as a result of elimination of risk of death from a disease from the population. Chiang (1968) has suggested a method for this purpose which could be applied when the current data on mortality by age for

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* Shukla, G.D. (1980). Personal Communication.

different diseases are available. In a country like ours, data on death rate by age due to all causes are hardly available in view of poor existing information system. In such a situation, estimation of impact of elimination of risk of death from a disease from the population on longevity poses a problem, indeed. Here, an effort has been made to estimate such an effect for malaria in the situations where current data on death rate due to all causes by age are not known. Further, despite the fact that communicable diseases are responsible for a major part of the total mortality, in our country such efforts have not been made thus far. The present communication is an attempt in this direction.

9.1 METHODOLOGY.

(I) General

In order to evaluate the impact of malaria eradication programme on longevity, it would be necessary first to calculate life expectancy in the presence of malaria. This, of course, can easily be obtained from ordinary Life Tables of the country. Another estimate of life expectancy can then be made assuming that malaria has been eliminated as a cause of death. This would, however, necessitate net

probabilities of death from malaria. The difference in these two life expectancies would be an estimate of the additional years of life that would be saved by an individual as a result of elimination of risk of death from malaria.

In fact, in human population, direct estimation of net probabilities is not possible. It may be estimated, however, as a part of problem of 'competing risk' or 'theory of multiple decrements'. The present problem represents a double decrement case where malaria represents one risk and the rest other causes, the other risk of death (Cornfield, 1957).

(II) Notations

Though, the notations used here are somewhat deviant from those considered conventionally, they have been introduced solely for the sake of convenience in the description.

x : Age of the individual.

n : Number of years between x to $x + n$.

${}_n^a x$: Proportion of life lived by those, aged x who die before reaching age $x + n$ in the interval $(x, x + n)$.

$_nM_x^m$: Age-specific death rate from malaria in the age interval (x, x + n).

$_nq_x$: Ordinary Life Table mortality function. Or, the probability that an individual alive at age x will die before reaching age x + n.

$_np_x$: $1 - {}_nq_x$.

$_nq_x^m$: Probability that an individual alive at age x will die of malaria before reaching age x + n in the presence of all other risks of death acting on the population. This is known as crude probability of death from malaria.

$_nq_x^o$: Probability that an individual alive at age x will die of causes other than malaria before reaching age x + n in the presence of risk of malaria. This is known as crude probability of death from the causes other than malaria.

$_nq_x^{(o)}$: Probability that an individual alive at age x will die before reaching age x + n if malaria is eliminated as a cause of death from the population. This is called net probability function.

e_x : Expectation of life at age x in the presence of risk of malaria.

$e_x^{(o)}$: Expectation of life at age x when malaria is eliminated as a cause of death.

(III) The Model

Let R^m and R^o be the risks of death from malaria and other causes respectively; they act simultaneously on each individual of the population. We consider following assumptions.

(i) Individuals of the populations are equally at the risk of death from malaria as well as from other causes.

(ii) The intensities of both the risks R^m and R^o are functions of age. We denote them by M_x^m and M_x^o respectively at age x.

(iii) Force of mortality from malaria in relation to the force of mortality from all other causes within each age interval (x, x + n) is constant.

Here, it may be seen that,

for all x, $M_x^m + M_x^o = M_x$ ----------(1)

Now, crude probability of death from malaria ${}_nq_x^m$ can be derived (Chiang, 1968) as,

$$ {}_nq_x^m = \frac{{}_nM_x^m}{{}_nM_x} \cdot {}_nq_x \qquad \text{----------(2)} $$

for all x, equations (1) and (2) imply that

$$ {}_nq_x^m + {}_nq_x^o = {}_nq_x \qquad \text{----------(3)} $$

Therefore,

$$ {}_nq_x^o = {}_nq_x - {}_nq_x^m \qquad \text{----------(4)} $$

When malaria has been eliminated as a cause of death, the net probability of death, ${}_nq_x^{(o)}$ can be obtained (Chiang, 1968) as,

$$ {}_nq_x^{(o)} = \left[1 - ({}_np_x)^{{}_nq_x^o/{}_nq_x} \right] \qquad \text{---------(5)} $$

From (4), equation (5) can be written as,

$$ {}_nq_x^{(o)} = \left[1 - ({}_np_x)({}_nq_x - {}_nq_x^m)/{}_nq_x \right] $$

Or,

$$ {}_nq_x^{(o)} = \left[1 - ({}_np_x)(1 - {}_nq_x^m / {}_nq_x) \right] \qquad \text{----(6)} $$

With ${}_nq_x$ and ${}_nq_x^{(o)}$ values being known for different x, the life expectancies in presence and absence of the

risk of death from malaria in the population can be worked-out. Here, it may be seen that because of competing risks, ${}_nq_x^{(o)} < {}_nq_x$ for different x.

Further, for all x,

$$e_x^{(o)} - e_x > 0 \quad \text{----------(7)}$$

Inequality (7) provides additional years of life that an individual of age x could expect to live if risk R^m is eliminated from the population. In other words, inequality (7) estimates the number of years of life lost to an individual of age x due to presence of risk of death from malaria in the population.

(IV) Estimation of parametric values

It may be seen that net probability function ${}_nq_x^{(o)}$ is dependant upon two probabilities, namely ${}_nq_x$ and ${}_nq_x^m$. The values of ${}_nq_x$ are known from the available abridged Life Table; problem is, thus, to estimate ${}_nq_x^m$. Such crude probabilities may be estimated from following well known function :

$${}_nq_x^m = \frac{n \cdot {}_nM_x^m}{1 + (a - {}_na_x)\, n \cdot {}_nM_x} \quad \text{----------(8)}$$

had the current data on crude death rates for all causes $({}_nM_x)$ been available to us for various age-intervals.

Since the data on ${}_nM_x$ for appropriate period for India are not available, on alternative method need to be considered.

Taking advantage of the relationship shown in (2), and putting value ${}_nM_x$ in (8), we have

$$ {}_nq^m_x = n \cdot {}_nM^m_x \left[1 - {}_nq_x (1-{}_na_x)\right] \quad \text{----------(9)} $$

The values of crude probability of death from malaria ${}_nq^m_x$ can now be obtained from (9) albeit the information on ${}_nM_x$ for different x, is not known.

Furthermore, values of ${}_nq^m_x$ can not be estimated from (9) for last age-interval which is half open, such as w years and above (In our case, this interval is 60 years and above), as length of interval is infinite and a_w is not known*.

Since, each one of l_w people alive at age w will eventually die, so $l_w = d_w$. The death rate for this open class-interval will, thus be,

$$ \hat{M}_w = \frac{l_w}{L_w} \quad \text{----------(10)} $$

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* w refers to the half open class interval; its various values are denoted by l_w, d_w, a_w, L_w and T_w etc.

Utilizing (2) and (10), the crude probability of death from malaria for last age-interval can be estimated from (11) given below.

$$\hat{q}^{m}_{w} = \frac{M^{m}_{w} \cdot q_{w}}{M_{w}}$$

Since $q_{w} = 1$,

$$\hat{q}^{m}_{w} = \frac{M^{m}_{w} \cdot L_{w}}{l_{w}} \qquad \text{----------(11)}$$

Furthermore, the estimation of $e^{(o)}_{w}$ would necessitate $L^{(o)}_{w}$ which is again not known. However, utilizing (1) and (10), it may be estimated from (12 given below.

$$\hat{L}^{(o)}_{w} = \frac{l_{w}}{M_{w} - M^{m}_{w}} \qquad \text{----------(12)}$$

9.2 NUMERICAL ILLUSTRATION.

In order to study the effect of malaria eradication on human longevity, the competing risk stochastic model, illustrated in Section 9.1 has been applied. Relevant epidemiological and demographic informations, available in the recent literature have been utilized for the purpose. The period of 15 years (1964-78) has been taken as the base for present analysis.

Table 9.1 shows reported malaria positive cases as well as annual parasite rates during 1964-1978 in India. The disease has shown increasing trend till the year 1976 when annual parasite rate of about 11% has been observed.

Since the data on actual number of malaria deaths are not available, an effort was made to estimate them using a set of assumptions regarding reporting efficiency, case fatality rate and age distribution of malaria deaths. Table 9.2 indicates that average number of malaria positive cases observed per year during the period considered has been 20,21,525 per year. This number has been inflated 10 times, based on the assumed reporting efficiency of 10%. In absence of any scientifically established ground, we considered this 10% reporting efficiency in malaria cases on the basis of our field experiences, and after discussing the issue with others*. Furthermore, our results on the extent of asymptomatic parasitaemia observed in the studied population (see, Chapter VIII) in association with many other factors viz. poor efficiency of malaria workers in collecting blood slides, low accuracy in their field

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* Shukla, G.D. (1980) : Personal Communication.

TABLE 9.1

Malaria positive cases and annual parasite index (A.P.I.) in India during 1964-1978).

Year	Malaria positive cases	Annual parasite index (A.P.I.)
1964	1,12,942	0.25
1965	99,667	0.22
1966	1,48,012	0.31
1967	2,78,214	0.57
1968	2,74,634	0.55
1969	3,47,975	0.68
1970	6,94,017	1.32
1971	13,22,398	2.47
1972	14,28,649	2.61
1973	19,30,273	3.46
1974	31,67,658	5.59
1975	51,66,142	9.10
1976	64,67,015	11.25
1977	47,40,900	7.56
1978	41,44,385	6,53

Source : Dutta and Bhasin (1979).

TABLE 9.2

Estimates of annual number of malaria positive cases and deaths from malaria in India.

S.No.	Specifications	Value of the estimates
1.	Average number of malaria positive cases per year.	20,21,525
2.	Reporting efficiency* of malaria cases.	10%
3.	Estimated malaria positive cases per year.	2,02,15,250
4.	Case fatality rate#	1.0%
5.	Estimated deaths from malaria per year.	2,02,153

Sources : * Shukla, G.D. (1980) : Personal Communication.

National Institute of Communicable Diseases (1976; 1977).

work and limitations of laboratory devices to prove the presence of malaria parasites in blood etc definitely give credence, to a great extent, to this our assumption. Assuming a case fatality rate of 1% (National Institute of Communicable Diseases, 1976; 1977), the average deaths from malaria were estimated to be 2,02,153 per year (Table 9.2).

Table 9.3 summarizes estimated annual deaths as well as population of India, and estimated age-specific deaths rates from malaria by age. Since the data on pattern of age distribution of malaria are not available for the present analysis, we assumed that age pattern of malaria deaths would be the same as that of malaria cases observed by us (Srivastava, et al, 1975). Based on these assumptions, the age and malaria specific mortality rates are estimated; an overall annual mortality rate of about 37/1,00,000 has, thus, been worked-out.

The complete Life Table for India (1961-70) had to be suitably abridged, following Chiang (1960; 1968) for both sexes combined, as abridged Life Table for India for relevant period were not available. Abridgement of complete Life Table has been shown in Table 9.4.

TABLE 9.3

Distribution of estimated malaria deaths and population by age and age-specific death rates from malaria per 1,00,000.

Age-group (year)	MALARIA DEATHS		Population**	Age specific death rate from malaria per 1,00,000.
	Proportion* (%)	Estimated annual deaths.		
Below 1	0.35	708	2,24,65,943	3.15
1 - 9	29.10	58,826	13,86,31,301	42.43
10 - 19	30.18	61,010	11,56,17,409	52.77
20 - 29	18.82	38,045	8,38,36,320	45.38
30 - 39	11.56	23,369	6,90,41,676	33.85
40 - 49	6.16	12,453	5,15,07,282	24.18
50 - 59	2.92	5,903	3,34,24,940	17.66
60 & over	0.91	1,839	3,34,24,938	5.50
Total	100.00	2,02,153	54,79,49,809	36.89

Sources : * Srivastava, et al (1975).

** Government of India (1974-75).

TABLE 9.4

Life Table# for India (1961-70), abridged* suitably for both sexes combined.

Age-group (year)	Number living at age x	Number dying in the interval (x to x+n)	Probability of dying in the interval (x to x+n)	Fraction of last age interval of life	Number of years lived in the interval (x to x+n)	Total years lived beyond age x	Expectation of life at age x
to x+n	l_x	nd_x	nq_x	na_x	nL_x	T_x	e_x
0 - 1	2,00,000	26,500	0.13250	0.25	1,80,125	92,73,789	46.37
1 - 9	1,73,500	16,202	0.09338	0.25	14,52,137	90,93,664	52.41
0 - 19	1,57,298	4,866	0.03094	0.51	15,49,137	76,41,527	48.58
0 - 29	1,52,432	7,758	0.05089	0.56	14,90,185	60,92,390	39.97
0 - 39	1,44,674	14,555	0.10061	0.56	13,82,690	46,02,205	31.81
0 - 49	1,30,119	21,557	0.16567	0.53	11,99,872	32,19,515	24.74
0 - 59	1,08,562	27,727	0.25540	0.52	9,52,530	20,19,643	18.60
0 & over	80,835	80,835	1.00000	-	10,67,113	10,67,113	13.20

Census of India (1971).

* Based on Complete Life Table for India (1961-70).

Tables 9.5 and 9.6, besides showing values of various Life Table functions also show the effect of elimination of malaria as a cause of death from the population on probability of death and on expectation of life respectively. Some decrease in probability of death as a result of elimination of risk of malaria has been seen in different age-groups; highest being of 16.56% in 10-19 years followed by 20-29 years (Table 9.5).

The life expectancy at birth for India during 1961-70 is estimated to be 46.37 years and 52.41 years in age-group 1-9 years. In absence of malaria, the estimated life expectancy at birth has been 46.98 years and 53.11 years in age-group 1-9 years. A gain in expected longevity at birth of 1.32% is estimated if malaria is eliminated as a cause of death from the population in India. Such gain for the age interval 1-9 years, however, is 1.34%. It may be seen that gains in the life expectancies of individuals as the result of elimination of malaria as a cause of death from the country is considerably higher for first 3 age-intervals than rest others. Further, such observations showed a decreasing trend in respect of gains with increasing age.

TABLE 9.5

Crude probability of death from malaria and effect of eliminating malaria as a risk of death from the population by age.

Age-group (year) x to x+n	$_nM_x^m$	$_nq_x^m$	$1 - \frac{_nq_x^m}{_nq_x}$	$_np_x$	$_nq_x^{(o)}$	$_nq_x - \frac{_nq_x^{(o)}}{_nq_x}$ (%)
< 1	0.0000315	0.0000284	0.9997857	0.86750	0.1324740	0.02
1 - 9	0.0004243	0.0035513	0.9619694	0.90662	0.0899936	3.62
10 - 19	0.0005277	0.0051970	0.8320297	0.96906	0.0258107	16.58
20 - 29	0.0004538	0.0044364	0.9128237	0.94911	0.0455859	10.42
30 - 39	0.0003385	0.0032352	0.9678442	0.89939	0.0975381	3.05
40 - 49	0.0002418	0.0022297	0.9865413	0.83433	0.1636336	1.23
50 - 59	0.0001766	0.0015495	0.9939331	0.74460	0.2540665	0.50
60 & over	0.0000550	0.0007261	0.9992739	0.00000	1.0000000	0.00

TABLE 9.6

Effect of eliminating malaria as a risk of death on expectation of life.

Age-group (year)	$_nq_x^{(o)}$	l_x	$_nd_x^{(o)}$	$_na_x$	$_nL_x^{(o)}$	$T_x^{(o)}$	$e_x^{(o)}$	$\frac{e_x^{(o)} - e_x}{e_x}$ (%)
< 1	0.13247	1,00,000	13,247	0.25	90,065	46,97,826	46.98	1.32
1 - 9	0.08999	86,753	7,807	0.25	7,28,080	46,07,761	53.11	1.34
10 - 19	0.02581	78,946	2,038	0.51	7,79,474	38,79,681	49.14	1.15
20 - 29	0.04558	76,908	3,505	0.56	7,53,658	31,00,207	40.31	0.85
30 - 39	0.09753	73,403	7,159	0.56	7,02,530	23,46,549	31.97	0.50
40 -- 49	0.16363	66,244	10,840	0.53	6,11,492	16,44,019	24.82	0.32
50 - 59	0.25407	55,404	14,076	0.53	4,86,475	10,32,527	18.64	0.22
60 & over	1.00000	41,328	41,328	-	5,46,052	5,46,052	13.21	0.08

9.3 DISCUSSION.

The present analysis is based on certain assumptions. It reveals, some effect of elimination of risk of death from malaria on probability of death as well as on expectation of life in India. However, the estimates are obviously subject to considerable variation because of limited data on which the major assumptions of the analysis are based.

Further, various assumptions, made herein, particularly on reporting efficiency and age distribution of malaria deaths, may also be questionable. It may, however, be pointed out that in India, Gelfand (1966) broughtforth an efficiency of 10% for smallpox. This, of course, gives some weightage to our assumption on reporting efficiency in malaria. Furthermore, many such debatable epidemiological values used in the analysis, undoubtedly limit the credibility of the results of the study.

However, even substantial variations in these assumptions would not alter the picture much and the general conclusion that elimination of malaria from India would result in the enhancement in life expectancy is not vitiated.

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SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

Formulation of mathematical models and their application to the various areas of medicine and health is a relatively newer concept. Use of such models in medical research can hardly be overemphasized in view of their utmost significance in the assessment of mortality and morbidity conditions, in the measurement of levels of health, in the planning and evaluation of health programmes and in studying the efficacy of drugs and transmission dynamics of the diseases etc. Mathematical models for some diseases, such as - cancer, filaria, tetanus, typhoid and endogenous depression etc are available.

Malaria, in India, is undoubtedly one of the worst scourges. The intensity of malaria transmission although not uniform all over the country has been considered the main obstacle to any type of control of the disease for the last few years. Many quantitative studies on malaria have recently been carried-out to study and interpret the malariometric data, however, the literature on mathematical modelling on the subject is still drastically scanty.

Furthermore, models available, if any, are mainly based on deterministic approaches and those based on probabilistic/stochastic approaches are negligible, indeed. Not only this, the available models, in general, are so complicated that their uses, by and large, seem to be difficult where computer facilities are not in abundance. With changing trends in malaria epidemiology, the patterns of disease should be studied utilizing present epidemiological knowledge with the help of random processes.

In the present work, an attempt has been made to formulate some mathematical models, based on stochastic processes, for studying certain epidemiological aspects of the disease. In order to illustrate their applicability and relative suitability, they have also been applied to the actual situations. Our observations, in nut shell, may be summarized as under.

1. Assessment of malaria situations in a population may be made by estimating malaria parasite incidence rate in infants who are considered to be negative for malaria at birth. A stochastic model for this purpose is discussed in Chapter IV. It also enables one to estimate the force of

malaria infection, acting on a population at any point of time. Application of the Life Table Method for estimating malaria parasite incidence rate for such populations from longitudinal data is also shown.

The two methods – stochastic model and Life Table method – were applied to a malariometric data concerning to a Keniyan population. Both the methods estimated the actual malaria situations in the population satisfactorily. The deviations in the results, if any, have been possibly because of limited details pertaining to the data available.

2. Malaria situations in a population of an area may also be studied by estimating parasite incidence and recovery rates from longitudinal data. In order to study such rates in the general population, a stochastic model with only two states – malaria positive state and malaria negative state has been suggested in Chapter V. It, inter alia, provides transition probabilities during a specified time from one state to the other. It was applied to the parasitological data, collected in a rural community of Jhansi district (U.P.).

Model indicated overall daily net malaria parasite incidence and recovery rates of 9/10,000 and 2% respectively indicating that, on an average, 9 persons per 10,000 population got fresh malaria infection in the area per day while 2 out of 100 'positives' got rid of it daily. Overall 'expected duration of positive episode' was observed to be of 43 days suggesting that 'positive' people of the area continued to suffer from the infection for a duration of about 43 days. Expected equilibrium parasite rate as well as the estimated transition probabilities from one state to the other for a period of one month were exactly the same as were actually observed in the area. This indicated that the evolved model is quite satisfactory for measuring actual malaria situations in a homogeneous population.

3. In longitudinal studies on malaria, the consideration of risk of 'lost to follow-up' of cases is important while estimating malaria transition rates. A model considering the presence of such a risk has been suggested in Chapter VI to estimate daily gross malaria parasite incidence and recovery rates.

The model was applied to the parasitological data; collected in a survey for the purpose (see, Chapter VIII). The overall daily gross malaria parasite incidence and recovery rates were estimated to be 8/10,000 and 26/1,000 respectively, indicating that 8 persons per 10,000 got malaria infection fresh per day and about 26 'positives' per 1,000 population of 'positives' got rid of the infection daily. The observed and expected probabilities of monthly transitions from one state to the other were almost same as were actually observed in the studied population indicating that the evolved model showed a good fit to the observational data.

4. In view of considerably different features of different malaria species, epidemiological patterns of the disease need to be studied by working-out malaria transition rates for different species separately. A stochastic model with 7 states is formulated in Chapter VII to estimate probabilities of transitions from one state to the other; it also allows one to study daily gross malaria parasite incidence and recovery rates for different species separately. The model is simple, practicable and the estimation of risk function matrix is also

quite easy. The application of the model is, however, not illustrated in view of non availability of the type of data required.

5. In order to study the applicability and suitability of models, evolved for estimating gross and net malaria parasite incidence and recovery rates in general populations from longitudinal data, the availability of relevant data is essential. When available literature on the subject did not provide, the type of data required in sufficient amount, a door-to-door study on malaria, consisting of one initial survey and two follow-ups at an average interval of 4 weeks was undertaken (see, Chapter VIII) in a rural community of Jhansi district (U.P.).

Out of 937 individuals studied initially, 32 cases were detected to be positive for malaria giving an overall malaria parasite rate of 3.42%. Furthermore, in males, about 62% individuals showed asymptomatic parasitaemia against 55% in case of females. Malaria parasite rates did not differ by age and sex. Only two species of the parasite, viz., P. vivax and P. falciparum were detected in the area with former playing a major role.

It would, indeed, be interesting to study the impact of the eradication of a particular disease from a population on the health of individuals residing therein. In Chapter IX, such an impact of malaria eradication on health has been studied in terms of expected longevity benefits. A stochastic model has been utilized to study the effects of the elimination of malaria from India, as a cause of death, on probability of death and on expectation of life of the individuals.

Application of the model utilizes data from different sources for India. The model indicates a gain in expected longevity at birth of 1.32%, if malaria is eliminated as a cause of death from the country. Such gain for age-group 1-9 years was 1.34%. Further, these gains were considerably higher for persons belonging to early ages than for those belonging to the later ages.

The models, broughtforth here, are based on certain assumptions and can be applied where certain conditions are met; however, they are useful for studying certain epidemiological patterns of malaria. The estimated values of some epidemiological parameters have their limitations

no doubt, but can be taken to be true for other communities of India resembling in nature with the present one. It is hoped that the present work would be of some use for health professionals, particularly those engaged in malaria control activities in India and elsewhere.

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APPENDIX

APPENDIX

A LONGITUDINAL STUDY ON MALARIA IN A RURAL COMMUNITY OF JHANSI DISTRICT (U.P.).

SCHEDULE OF SURVEY

(a) General :

Name of the village ..... Date .....

Name of the head of the family .....

Family code No. .....

Name of the individual .....

Individual Code No. .....

Age (years) ..... Sex .....

Occupation : Agriculture/ Business / Labour /
Skilled profession / Housework /
Student / Child / Any other (specify)...

Literacy status : Illiterate / Just literate /
Primary / J.H.S. / H.S. / Intermediate /
Graduate or more.

Monthly family income : .....

Total family monthly income .....

Social Class : I / II / III / IV / V.

(b) Details of first survey :

Complete address of stay during last one month : .....
.....

Malaria symptoms present : Yes / No.

If yes, give history :

Fever for the last ..... days

Rigor : Yes / No.

Periodicity : Daily / Alternate / Continuous.

Other details

Spleenomegaly : Present / Absent.

Mosquitoe breeding places in and around the house : Present / Absent.

Report of blood examination :

Thick smear : Positive / Negative.

Thin smear : Positive / Negative.

Species : P.vivax / P.falciparum / P.malariae / Others (specify)

Details of treatment given, if any. : .....

.....

(c) Details of second survey :

Date of second survey : .....

Duration between two consecutive surveys (in days) : .....

Complete address of stay during last one month : .....

.....

Malaria symptoms present : Yes / No

If yes, give history :

Fever for the last ..... days.

Rigor : Yes | No

Periodicity : Daily / Alternate / Continuous.

Other details :

Spleenomegaly : Present / Absent

Mosquitoe breeding places in and around the house : Present / Absent

Report of blood examination

Thick smear : Positive / Negative

Thin smear : Positive / Negative

Species : P.vivax / P.falciparum / P.malariae / Others.

Details of treatment given, if any : .....

.....

(d) Details of the third survey:

Date of third survey : .....

Duration between two consecutive surveys (in days) : .....

Complete address of stay during last one month : .....

.....

.....

Malaria symptoms present : Yes / No

If yes, give history :

Fever for the last ..... days.

Rigor : Yes / No

Periodicity : Daily / Alternate / Continuous.

Other details :

Spleenomegaly : Present / Absent

Mosquitoe breeding places in and around the house : Present / Absent

Report of blood examination:

Thick smear : Positive / Negative

Thin smear : Positive / Negative

Species : P.vivax / P.falciparum / P.malariae / Others.

Details of treatment given, if any : .....

.....

Signature of Lab. Technician.

Signature of Investigator.

Checked by : ..... Dated : .....

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